was 670 metric tons (1.5 million pounds) in 1999, 460 metric tons (1 million pounds) in 2000, 31 metric tons (68,000 lb) in 2001, and 33 metric tons (73,000 lb) in 2002 (Plachy 2000, 2002). No more recent data on production of cadmium compounds were found.

Eight U.S. companies were identified as major producers of cadmium compounds in the 1990s (ATSDR 1999). Only three U.S. companies were reported to have produced refined cadmium in 2009 (Tolcin 2009a). One company recovered cadmium as a by-product of zinc leaching from roasted sulfide concentrates, and the other two companies thermally recovered cadmium metal from spent NiCd batteries and other cadmium-bearing scrap. In 2010, 15 U.S. suppliers of cadmium metal, 13 suppliers of cadmium metal powder, and numerous suppliers of various cadmium compounds were identified (ChemSources 2010).

U.S. imports of cadmium fell over the late 20th century and early 2000s. Annual cadmium imports averaged 694 metric tons (1.5 million pounds) in the 1960s, 2,088 metric tons (4.6 million pounds) in the 1970s, 2,524 metric tons (5.6 million pounds) in the 1980s, 1,156 metric tons (2.5 million pounds) in the 1990s, and 216 metric tons (476,000 lb) in the 2000s. For 2009, U.S. imports of cadmium were estimated to be 194 metric tons (428,000 pounds). Annual U.S. exports averaged 425 metric tons (937,000 lb) in the 1960s, 188 metric tons (414,000 lb) in the 1970s, 211 metric tons (465,000 lb) in the 1980s, 454 metric tons (1 million pounds) in the 1990s, and 425 metric tons (937,000 lb) in the 2000s. For 2009, U.S. exports were estimated to be 676 metric tons (1.5 million pounds) (Tolcin 2009a, USGS 2009).

Exposure

The general population may be exposed to cadmium through consumption of food and drinking water, inhalation of cadmium-containing particles from ambient air or cigarette smoke, or ingestion of contaminated soil and dust. Tobacco smokers are exposed to an estimated 1.7 µg of cadmium per cigarette. Food is the major source of cadmium exposure for nonsmokers; average cadmium levels in the U.S. food supply range from 2 to 40 ppb. The daily adult intake of cadmium is estimated to be approximately 30 µg, with the largest contribution from grain cereal products, potatoes, and other vegetables. Exposures through drinking water or ambient air typically are very low (ATSDR 1999).

The U.S. Environmental Protection Agency's Toxics Release Inventory (TRI) collects cadmium data in two categories, "cadmium" and "cadmium compounds," and individual facilities may report releases in both categories. From 1988 to 1997, reported releases of cadmium to the environment ranged from about 106,000 to 635,000 lb and releases of cadmium compounds from about 825,000 to 4.1 million pounds. Since 1998 (when the number of industries covered by the TRI was increased), cadmium releases have ranged from a low of about 740,000 lb in 2000 to a high of about 2.8 million pounds in 1998. In 2007, 34 facilities reported releasing about 940,000 lb of cadmium, most of which was released to land on site. Reported releases of cadmium compounds since 1998 have ranged from a low of nearly 8.9 million pounds in 2000 to 3.15 million pounds in 2007, reported by 73 facilities, most of which was released to land on site (TRI 2009).

Workers in a wide variety of occupations potentially are exposed to cadmium and cadmium compounds (IARC 1993). Occupations with the highest potential levels of exposure include smelting zinc and lead ores, welding or remelting cadmium-coated steel, working with solders that contain cadmium, and producing, processing, and handling cadmium powders. The major routes of occupational exposure are inhalation of dust and fumes and incidental ingestion of dust from contaminated hands, cigarettes, or food (ATSDR 1999). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 250,000 workers potentially were exposed to cadmium and selected inorganic cadmium compounds. These included workers potentially exposed to unknown cadmium compounds (88,968), cadmium sulfide (42,562), cadmium mercury sulfide (19,707), cadmium selenide (17,939), cadmium oxide (15,727), cadmium chloride (4,748), cadmium nitrate (1,878), and cadmium sulfate (1,313) (NIOSH 1990). The Occupational Safety and Health Administration estimated in 1990 that about 512,000 U.S. workers were exposed to cadmium; however, 70% to over 80% were exposed to cadmium at concentrations below the limits set by occupational standards or guidelines (ATSDR 1999).

Regulations

Department of Transportation (DOT)

Cadmium is considered a hazardous material, and cadmium compounds are considered both hazardous materials and marine pollutants, and requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Cadmium compounds are listed as a hazardous air pollutant.

New Source Performance Standards: Regulations have been developed to limit cadmium emissions from new municipal waste combustion units.

Urban Air Toxics Strategy: Cadmium compounds have been identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Cadmium acetate, cadmium bromide, and cadmium chloride are designated as hazardous substances.

Limits have been established for cadmium in biosolids (sewage sludge) when used or disposed of via land application or incineration.

Effluent Guidelines: Cadmium and cadmium compounds are listed as toxic pollutants.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for cadmium, cadmium acetate, cadmium bromide, cadmium chloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cadmium and cadmium compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 100 lb for cadmium oxide; = 1,000 lb for cadmium stearate.

Threshold planning quantity (TPQ) = 100 lb for cadmium oxide solids in powder form particle size < 100 µm or solution or molten form; = 1,000 lb for cadmium stearate in powder form particle size < 100 µm or solution or molten form; = 10,000 lb for cadmium oxide and cadmium stearate in all other forms.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for cadmium chloride have been cancelled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 1.0 mg/L for cadmium.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of cadmium = F006, K061, K064, K069, K100.

Cadmium and cadmium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L (cadmium).

Food and Drug Administration (FDA)

Maximum permissible level of cadmium in bottled water = 0.005 mg/L.

Various specified color additives may contain cadmium at levels no greater than 15 ppm.

Specified food additives may contain cadmium at maximum levels that range from 0.05 to 0.13 ppm.

Action levels for cadmium in pottery (ceramics) range from 0.25 to 0.5 µg/mL leaching solution.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Ceiling concentration = 0.3 mg/m^3 for cadmium fume; = 0.6 mg/m^3 for cadmium dust.

Permissible exposure limit (PEL) = 0.005 mg/m^3 for cadmium dust and fume.

Comprehensive standards for occupational exposure to cadmium and cadmium compounds have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 mg/m^3; = 0.002 mg/m^3 for respirable fraction.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 9 mg/m^3 for cadmium dust and fume. Cadmium dust and fume are listed as potential occupational carcinogens.

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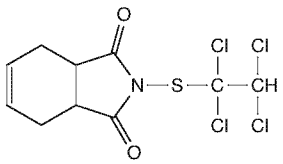
Captafol

CAS No. 2425-06-1

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Difolatan (formerly a registered trademark of Chevron Chemical Company)



Carcinogenicity

Captafol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data on mechanisms of carcinogenesis.

Cancer Studies in Experimental Animals

Oral exposure to captafol caused tumors at several different tissue sites in rats and mice. Long-term feeding studies were conducted with two mouse strains (CD-1 and B6C3F$_1$) (Ito *et al.* 1984, Quest *et al.* 1993, NTP 2008) and two rat strains (Crl:CD and F344) (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993, NTP 2008). In mice of both sexes, tumors were predominantly of the vascular system, gastrointestinal system, and liver; they included (1) cancer of the lymphoid tissue (lymphosarcoma) in CD-1 mice, (2) blood-vessel cancer (hemangiosarcoma) in B6C3F$_1$ and CD-1 mice, (3) benign tumors of blood vessels of the spleen (splenic hemangioma) in B6C3F$_1$ mice, (4) benign and malignant tumors of the small intestine in B6C3F$_1$ mice, and (5) liver cancer (hepatocellular carcinoma) in B6C3F$_1$ mice. Benign Harderian-gland tumors (adenoma) also were observed in CD-1 males (Ito *et al.* 1984, Quest *et al.* 1993). In rats, captafol caused liver and kidney tumors in several studies and benign mammary-gland tumors (fibroadenoma) in female Crl:CD rats in one study (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993). Benign liver tumors (hepatocellular adenoma) were observed in female Crl:CD rats and in F344 rats of both sexes, and a significant dose-related trend was observed for malignant liver tumors (hepatocellular carcinoma) in female F344 rats (Tamano *et al.* 1990, Quest *et al.* 1993, NTP 2008). Captafol caused benign kidney tumors (renal-cell adenoma) in F344 rats of both sexes and malignant kidney tumors (renal-cell carcinoma) in F344 males (Nyska *et al.* 1989, Tamano *et al.* 1990). In Crl:CD rats, the combined incidence of benign and malignant kidney tumors (renal-cell adenoma and carcinoma) was increased in males, and a significant dose-related trend was observed for malignant kidney tumors (renal-cell carcinoma) in both sexes (Quest *et al.* 1993, NTP 2008.)

Captafol was shown to be hepatotoxic and to induce potentially preneoplastic glutathione S-transferase placental form positive (GST-P+) foci in the liver of male F344 rats (NTP 2008) in both the initiation and promotion phases of studies of tumor development. In addition, promotion with captafol increased the incidences of hyperplasia of the forestomach and adenoma of the small intestine (Uwagawa *et al.* 1991), thyroid follicular-cell adenoma (Ito *et al.* 1996), and the expression of a marker of cell proliferation (proliferating-cell nuclear antigen) in the kidney (Kim *et al.* 1997) in F344 rats.

Studies on Mechanisms of Carcinogenesis

In rodents, captafol is absorbed through the gastrointestinal tract and lung and to a lesser extent through the skin; however, the available data indicate that captafol and its metabolites do not accumulate in the tissues of animals and are rapidly eliminated, primarily in the urine. The metabolism and disposition of captafol after oral absorption is anticipated to be similar in experimental animals and humans (NTP 2008). Two metabolic pathways, based primarily on oral absorption, have been proposed; one pathway involves reaction of captafol with cellular thiol-containing molecules such as glutathione and cysteine, and the other involves hydrolysis of the N–S bond. Both pathways are relevant to the mechanism of carcinogenesis, as the reaction of captafol with thiol groups can lead to cytotoxicity, and metabolites derived from the side chain have been shown to be carcinogenic. Tetrahydrophthalimide is a product of both reaction pathways and has been identified in blood, urine, and feces of rats, dogs, and monkeys (Hayes 1982). However, tetrahydrophthalimide has not been tested in carcinogenicity bioassays. Dichloroacetic acid (previously shown to be carcinogenic in mice) was identified as a minor metabolite of captafol in rodents (NTP 2008). Another reported metabolite of captafol is 2-chloro-2-methyl-thioethylene sulfonic acid (which is derived from the side chain) (IPCS 1990). The proposed mechanism for formation of this metabolite is through transient formation of an episulfonium ion, a DNA alkylating agent (IPCS 1990, Williams 1992, Bernard and Gordon 2000).

Short-term *in vitro* and *in vivo* genotoxicity studies support mutagenicity as a mechanism of carcinogenesis. Captafol is an alkylating agent and has produced genotoxic effects in a variety of systems (NTP 2008). It caused mutations in *Salmonella typhimurium* (base-pair mutations) and *Escherichia coli* and in non-mammalian *in vivo* systems (*Aspergillus nidulans* and *Drosophila melanogaster*). In *in vitro* studies with cell lines from rodents and other mammals, captafol caused DNA single-strand breaks, sister chromatid exchange, chromosomal aberrations, micronucleus formation, polyploidy (in one of two studies), mitotic spindle disturbances, and cell transformation. In human cells *in vitro*, it caused DNA single-strand breaks, sister chromatid exchange, micronucleus formation, and chromosomal aberrations. In rodents exposed *in vivo*, captafol caused DNA strand breaks, micronucleus formation (Robbiano *et al.* 2004), and dominant lethal mutations in rats (Collins 1972) but did not cause mutations in the host-mediated assay in rats or dominant lethal mutations in albino mice (Kennedy *et al.* 1975).

In addition to direct genotoxic activity, epigenetic mechanisms, such as cytotoxicity as a result of reduced cellular content of thiol groups (nonprotein and protein), inhibition of enzymes involved in DNA replication (DNA topoisomerases and polymerases), inhibition of DNA and RNA synthesis, and induction of cytochrome P450 mono-oxygenases may also be involved in the pathogenesis of tumor formation (NTP 2008).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to captafol. One case-control study (Clary and Ritz 2003) directly addressed captafol exposure. This study was based upon an ecologic (group-level) exposure assessment and included 17 other chlorinated pesticides. A statistically nonsignificant increase in pancreatic cancer was reported among residents who had lived for over 20 years in geographical areas with high captafol use; however, confounding by other cancer risk factors could not be ruled out, and the study was limited by imprecise measures of exposure and diseases.

Properties

Captafol is a broad-spectrum nonsystemic fungicide that is categorized as a phthalimide fungicide based on its tetrahydrophthalimide chemical ring structure (other phthalimide fungicides include captan and folpet). Captafol exists as white, colorless to pale-yellow, or tan (technical grade) crystals or as a crystalline solid or powder, with a slight characteristic pungent odor. It is practically insoluble in water but is soluble or slightly soluble in most organic solvents. Captafol reacts with bases, acids, acid vapors, and strong oxidizers (HSDB 2010). It hydrolyzes slowly in aqueous emulsions or suspensions, but rapidly in acidic and basic aqueous alkaline media (Akron 2010). Captafol will not burn, but when heated to decomposition, it emits toxic fumes, including nitrogen oxides, sulfur oxides, phosgene, and chlorine (IPCS 1993). Physical and chemical properties of captafol are listed in the following table.

Property	Information
Molecular weight	349.1[a]
Density	1.64 ± 0.1 g/cm^3 at 20°C (calculated from molar volume)[b]
Melting point	160°C to 161°C (decomposes slowly)[c]
Log K_{ow}	3.8 at 25°C[a]
Water solubility	1.4 mg/L at 20°C; 2.24 mg/L at 25°C[d]
Vapor pressure (mm Hg)	8.27×10^{-9} at 20°C[d]
Vapor density relative to air	12[e]
Dissociation constant (pK_a)	–2.67 ± 0.20 at 25°C[b]

Sources: [a]HSDB 2010, [b]CAS 2008, [c]BCPC 2006, [d]Kim *et al.* 1997, [e]Akron 2010.

Use

Captafol is a nonsystemic fungicide used to control fungal diseases of fruits, vegetables, ornamental plants, and grasses and as a seed treatment. It also was used in the timber industry to control woodrot fungi on logs and wood products (IARC 1991, IPCS 1990). Captafol was produced and used as a fungicide in the United States until 1987, when all registrants of captafol products requested voluntary cancellation of their registrations. Legal use of existing stocks was allowed after 1987; however, in 1999, the U.S. Environmental Protection Agency further restricted its use, and all captafol tolerances were revoked except those for onions, potatoes, and tomatoes. These remaining tolerances were revoked in 2006. Although many countries banned its use, captafol was still used as of the mid 2000s in several countries that exported agricultural products to the United States, including Mexico and Brazil; however, by 2010, no countries were identified that still allowed the use of captafol on food crops.

Production

Captafol is produced by the reaction of tetrahydrophthalimide and 1,1,2,2-tetrachloroethylsulfenyl chloride in the presence of aqueous sodium hydroxide (IARC 1991). It was first registered and produced commercially in the United States in 1961 as Difolatan (IPCS 1993). From 1979 to 1981, annual U.S. production of captafol was estimated to be 3,600 to 4,500 metric tons (8 million to 10 million pounds) (as active ingredient), of which about half was exported (IARC 1991). In 1983, captafol was produced by one U.S. company, whose annual pro-

duction capacity was 12 million pounds (SRI 1984). Production in 1985 was estimated at 6,600 metric tons (14.5 million pounds) (IARC 1991). In 2010, no producers of captafol were identified worldwide (SRI 2010), but Difolatan (a captafol fungicide) was available from ten suppliers, including five in the United States, one in France, one in Hong Kong, two in India, and one in South Africa. In addition, Captafol Pestanal (an analytical standard for captafol) was available from two U.S. suppliers and one Swiss supplier (Chem Sources 2010).

Exposure

In the past, exposure to captafol occurred by ingestion, inhalation, or dermal contact. The potential for exposure of both the general population and agricultural workers would have been greatest from the late 1970s through the mid 1980s, when annual domestic usage was estimated to be at least 4 million pounds. In the past, the general population was potentially exposed to captafol through ingestion of contaminated groundwater or agricultural products sprayed with captafol, through exposure to topsoil, or through its application in nearby agricultural settings. In the United States, captafol was no longer produced after 1987 or used after 2006. It is possible, though highly unlikely, that individuals could be exposed by ingestion of imported fruits or vegetables treated with captafol. The U.S. Food and Drug Administration's Pesticide Residue Monitoring Program and the U.S. Department of Agriculture's Pesticide Data Program detected captafol at low levels in food samples in the 1980s and 1990s, but have not detected it since 1998. No captafol residues were detected in the FDA's Total Diet Study (FDA 1988, 1989, 1993, Yess *et al.* 1993, Gunderson 1995). Between 1993 and 2003, captafol was detected once in animal feed, at a concentration of 0.036 ppm in a barley sample from Maryland in 1999 (FDA 2000).

In air, captafol is expected to exist solely in the particulate phase, based on its vapor pressure; however, some reports suggest that it exists in the vapor phase. In water, captafol is expected to adsorb to sediment and suspended solids. In soil, captafol is expected to have slight mobility, based on its soil organic carbon–water partition coefficient (HSDB 2010). Volatilization from soil is not expected to be an important fate process. Reported values for captafol's half-life soil vary among sources, ranging from less than 3 days to around 11 days (Extoxnet 1995, HSDB 2010). Captafol has been detected in the vicinity of agricultural uses outside the United States; it was detected in air in Canada (Frank *et al.* 1994), in surface water in Spain (Picó *et al.* 1994, Vioque-Fernandez *et al.* 2007) and Italy (Readman *et al.* 1997), and in soil in India (Venkatramesh and Agnihothrudu 1988). Runoff losses of captafol with natural rainfall were less than 0.1% of the amount applied (Kim *et al.* 1996).

U.S. workers previously were exposed to captafol during its production, formulation, or application to agricultural fields; on reentry to a sprayed field; or when working with treated timber products (IPCS 1993, HSDB 2010). In a study of worker exposure to Difolatan 80 Sprills (80% captafol) in central Florida orange groves, aerosolized captafol concentrations averaged 56 $\mu g/m^3$ for mixer-loaders and 34 $\mu g/m^3$ for spray applicators. Hourly dermal exposure levels were approximately 1 to 10 $\mu g/cm^2$ for the hands, legs, and arms; however, levels of up to 20 $\mu g/cm^2$ were seen when direct contact with captafol solution was evident. Whole-body exposures ranged from 15 to 116 mg/h, with a mean of 40 mg/h; the hands accounted for about 40% of total exposure (Popendorf 1988).

Captafol toxicity was reported in exposed workers. Peoples *et al.* (1978) presented 37 brief case reports of exposure during the manufacture and application of captafol that had been reported to the California Department of Food and Agriculture from 1974 through 1976. The reports reflected toxic outcomes of possible captafol exposure that were reported by physicians, including systemic, skin, and eye toxicity. Positive patch tests for captafol or a history of occupationally induced dermatitis were reported in studies of workers who packed captafol (Camarasa 1975), workers exposed to captafol in timber-treatment plants (Stoke 1979), agricultural workers and former agricultural workers (Lisi *et al.* 1986, 1987, Guo *et al.* 1996, Rademaker 1998), flower-shop workers (Thiboutot *et al.* 1990), and laboratory chemists (Brown 1984).

Regulations

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Limitations: Daily discharge maximum = 4.24×10^{-6} kg/kkg (kg/metric ton); monthly average discharge maximum = 1.31×10^{-6} kg/kkg.

Federal Insecticide, Fungicide, and Rodenticide Act

Classified as Group B, probable human carcinogen based on mammary-gland and liver tumors in female Sprague-Dawley rats, kidney tumors in both male and female rats, and lymphosarcoma and hemangiosarcoma in both male and female CD-1 mice, with Harderian-gland tumors in male mice.

Food and Drug Administration (FDA)

Tolerance levels have been revoked for all foods, thereby making it illegal to import or introduce into commerce any foods with captafol residue.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 mg/m^3.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.
Recommended exposure limit (REL) = 0.1 mg/m^3.

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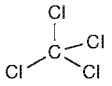
Carbon Tetrachloride

CAS No. 56-23-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as tetachloromethane



Carcinogenicity

Carbon tetrachloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Carbon tetrachloride caused tumors in several species of experimental animals, at two different tissue sites, and by several different routes of exposure. It caused benign or malignant liver tumors when administered (1) orally in mice and rats of both sexes, in hamsters, and in trout, (2) by subcutaneous injection in male rats, and (3) by inhalation in rats (of unspecified sex) (IARC 1972, 1979). Subcutaneous injection of carbon tetrachloride caused benign and malignant mammary-gland tumors (fibroadenoma and adenocarcinoma) in female rats.

Since carbon tetrachloride was listed in the *Second Annual Report on Carcinogens*, additional studies in mice have been identified. Inhalation exposure to carbon tetrachloride caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) and benign adrenal-gland tumors (pheochromocytoma) in mice of both sexes (Nagano *et al.* 1998, 2007, IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to carbon tetrachloride. Three cases of liver cancer were reported in humans with cirrhosis of the liver who had been exposed to carbon tetrachloride (IARC 1979).

After carbon tetrachloride was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies were identified and reviewed by the International Agency for Research on Cancer. IARC (1999) concluded that there was inadequate evidence in humans for the carcinogenicity of carbon tetrachloride. Statistically nonsignificant increased risks for non-Hodgkin's lymphoma in association with potential exposure to carbon tetrachloride were found among female aircraft-maintenance workers (Blair *et al.* 1998) and in a nested case-control study of rubber workers (Checkoway *et al.* 1984, Wilcosky *et al.* 1984). The latter study also found an increased risk of leukemia. Studies on drycleaning workers were not specific for exposure to carbon tetrachloride (Blair *et al.* 1990, 1993), and IARC considered the population-based case-control studies to be uninformative (IARC 1999).

Since the 1999 IARC review, additional studies have been identified that evaluated the relationship between non-Hodgkin's lymphoma and carbon tetrachloride exposure. Statistically significant risks of non-Hodgkin's lymphoma were reported among individuals with potential exposure to carbon tetrachloride used as a pesticide (McDuffie *et al.* 2001) and among women occupationally exposed to carbon tetrachloride (Wang *et al.* 2009). A small, statistically nonsignificant excess of non-Hodgkin's lymphoma was also found among laboratory workers potentially exposed to carbon tetrachloride and other agents (Kauppinen *et al.* 2003). In an extended follow-up of

the cohort of female aircraft-maintenance workers exposed to carbon tetrachloride, the risk of non-Hodgkin's lymphoma was lower than in the earlier study, although still (nonsignificantly) elevated (Radican *et al.* 2008).

Properties

Carbon tetrachloride is a halomethane that exists at room temperature as a clear, colorless, heavy liquid with a sweetish, aromatic, moderately strong ethereal odor. It is very slightly soluble in water, soluble in ethanol and acetone, and miscible with benzene, chloroform, ether, carbon disulfide, petroleum ether, and oils. It is nonflammable and is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of carbon tetrachloride are listed in the following table.

Property	Information
Molecular weight	153.8
Specific gravity	1.594 at 20°C/4°C
Melting point	–23°C
Boiling point	76.8°C
Log K_{ow}	2.83
Water solubility	793 mg/L at 25°C
Vapor pressure	115 mm Hg at 25°C
Vapor density relative to air	5.32

Source: HSDB 2009.

Use

Carbon tetrachloride is used as a chemical intermediate and as a feedstock in the production of chlorofluorocarbons, such as the Freons dichlorodifluoromethane (F-12) and trichlorofluromethane (F-11), which are used primarily as refrigerants. It is also used in petroleum refining, in pharmaceutical manufacturing, as an industrial solvent, in the processing of fats, oils, and rubber, and in laboratory applications (IARC 1999, ATSDR 2005, HSDB 2009). It currently is not permitted in products intended for home use (HSDB 2009). Until the mid 1960s, carbon tetrachloride was used as a cleaning fluid both in industry and in the home (in spot removers) and in fire extinguishers (ATSDR 2005). It was also used as a grain fumigant until 1986, when its use for this purpose was cancelled by the U.S. Environmental Protection Agency. Other previous uses include as a rodenticide, as a solvent in some household products, in the formulation of gasoline additives, and in metal recovery and catalyst regeneration (ATSDR 2005, HSDB 2009). In the early 1900s, it was used in human medicine to destroy intestinal parasitic worms, and it was used for a short period as an anesthetic (IARC 1972, ATSDR 2005).

Production

Large-scale U.S. production of carbon tetrachloride began in 1907 (IARC 1979). In 2009, carbon tetrachloride was produced by 26 manufacturers worldwide, including 3 in the United States (SRI 2009), and was available from 69 suppliers, including 19 U.S. suppliers (ChemSources 2009). U.S. imports of carbon tetrachloride totaled 110 million kilograms (242 million pounds) in 1989, decreasing to zero 1996; since 1996, only 41 kilograms (90 lb) has been imported. U.S. exports of carbon tetrachloride decreased from 52.7 million kilograms (116 million pounds) in 1989 to 1.7 million kilograms (3.8 million pounds) in 2008 (USITC 2009).

Exposure

The primary routes of potential human exposure to carbon tetrachloride are inhalation, ingestion, and dermal contact. The general population is most likely to be exposed to carbon tetrachloride through air and drinking water. In 1988, EPA's Toxics Release Inventory listed 95 industrial facilities that produced, processed, or otherwise used carbon tetrachloride and reported environmental releases of carbon tetrachloride totaling 3.9 million pounds (TRI 2009). In 1990, 1.7 million pounds was released to air, 36,201 lb to water, and a little over 1,000 lb to soil (ATSDR 2005). In 1999, on-site releases totaled 268,140 lb, and in 2007, 308,633 lb was released by 44 facilities, mostly to underground injection wells or to air (TRI 2009).

Carbon tetrachloride is also formed in the troposphere by solar-induced photochemical reactions of chlorinated alkenes. Because it is readily volatile at ambient temperature and degrades very slowly, it has gradually accumulated in the environment. It is broken down by chemical reactions in air, but so slowly that its estimated atmospheric lifetime is between 30 and 100 years, with 50 years generally regarded as the probable value. In 1988, the average concentration of carbon tetrachloride in air in the United States was reported to be 0.168 ppb, and other studies have observed a steady increase in global atmospheric levels at an annual rate of about 1.3% (IARC 1979). EPA estimated that 8 million people living within 12.5 miles of manufacturing sites were possibly exposed to carbon tetrachloride at an average concentration of 0.5 μg/m^3 and a peak concentration of 1,580 μg/m^3. Point sources of carbon tetrachloride from industry and wind direction are responsible for localized increases in air concentration (ATSDR 2005). A recent study found that during the use of chlorine bleach in cleaning bathrooms and kitchen surfaces, the indoor air concentration of carbon tetrachloride reached 55 μg/m^3; even after 30 minutes, it was measured at 23 μg/m^3 (Odabasi 2008). Based on a typical carbon tetrachloride concentration in ambient air of about 1 μg/m^3 and assuming inhalation of 20 m^3 of air per day by a 70-kg adult and 40% absorption of carbon tetrachloride across the lung, daily inhalation exposure has been estimated at 0.1 μg/kg of body weight (ATSDR 2005).

Exposure to carbon tetrachloride may also occur by dermal contact with tap water (e.g., during bathing) (ATSDR 2005). Surveys have found that about 99% of all groundwater supplies and 95% of all surface-water supplies contain carbon tetrachloride at a concentration of less than 0.5 μg/L. Exposure to carbon tetrachloride by ingestion may occur through consumption of contaminated drinking water or food. In a study of New Jersey tap water, the maximum monthly estimated concentration of carbon tetrachloride was 7 μg/L, based on measurements by utilities (Bove *et al.* 1995). Based on a typical carbon tetrachloride concentration of 0.5 μg/L in drinking water, daily consumption of 2 L of water by a 70-kg adult yields an estimated daily intake of about 0.01 μg/kg of body weight (ATSDR 2005). Exposure from contaminated food is possible, but it is not likely to be of much significance, because levels of carbon tetrachloride in most foods are below the limit of detection. In the U.S. Food and Drug Administration's Total Diet Study, carbon tetrachloride was detected in 41 of 1,331 samples (3%) of 37 food items (FDA 2006). The highest measured concentration was 0.031 mg/kg in one sample of smooth peanut butter, and carbon tetrachloride was detected in two samples of boiled beef frankfurters. Carbon tetrachloride might have been ingested as a contaminant of foods treated before its use as a grain fumigant was banned; in treated stored grain, it was detected at concentrations ranging from 1 to 100 mg/kg (ATSDR 2005).

The greatest risk of occupational exposure to carbon tetrachloride most likely occurred during its use as a fumigant. According to the National Institute for Occupational Safety and Health, the workers most likely to be exposed to carbon tetrachloride are employed at blast furnaces and steel mills, in the air transportation industry, and in motor vehicle and telephone and telegraph equipment manufacturing. It was estimated that 4,500 workers potentially were exposed during production of carbon tetrachloride and 52,000 during

its industrial use. The Occupational Safety and Health Administration estimated that 3.4 million workers potentially were exposed to carbon tetrachloride directly or indirectly. Exposure to carbon tetrachloride may occur in drycleaning establishments, where its concentration in ambient air was found to average between 20 and 70 ppm. Average exposures of 206 and 338 ppm, with excursions to 1,252 and 7,100 ppm, were reported during operation of drycleaning machines. Occupational exposure may also occur during its use in the manufacture of F-11 and F-12. Exposure during fluorocarbon production is most likely for tank-farm and process operators, who may be exposed to emissions from storage-tank vents, from process-equipment leaks or spills, or resulting from transfer of the chemical (NCI 1985). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 77,315 workers, including 12,605 women, potentially were exposed to carbon tetrachloride (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of carbon tetrachloride on ships and barges.

Consumer Product Safety Commission (CPSC)

Carbon tetrachloride and mixtures containing it (with the exception of chemicals containing unavoidable residues of carbon tetrachloride that do not result in atmospheric concentrations of carbon tetrachloride greater than 10 ppm) are banned from consumer products.

Department of Transportation (DOT)

Carbon tetrachloride is considered a hazardous material and marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of carbon tetrachloride is subject to certain provisions for the control of volatile organic compound emissions.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.
Carbon tetrachloride is regulated as a Class I substance for stratospheric ozone protection.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.23 µg/L; based on fish or shellfish consumption only = 1.6 µg/L.
Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for use as a pesticide have been cancelled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of carbon tetrachloride = U211, F001, F024, F025, K016, K019, K020, K021, K073, K116, K150, K151, K157.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.
All medical devices containing or manufactured with carbon tetrachloride must contain a warning statement that the compound may destroy ozone in the atmosphere.

Mine Safety and Health Administration

Carbon tetrachloride use is banned in metal and non-metal surface and underground mines.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 10 ppm.
Ceiling concentration = 25 ppm.
Acceptable peak exposure = 200 ppm (maximum duration = 5 min in any 4 h).
Carbon tetrachloride can not be used as a fire extinguishing agent where employees may be exposed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 5 ppm.
Threshold limit value – short-term exposure limit (TLV-STEL) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Short-term exposure limit (STEL) = 2 ppm (12.6 mg/m^3) (60-min exposure).
Immediately dangerous to life and health (IDLH) limit = 200 ppm.
Listed as a potential occupational carcinogen.

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Ceramic Fibers (Respirable Size)

CAS No.: none assigned

Reasonably anticipated to be human carcinogens

First listed in the *Seventh Annual Report on Carcinogens* (1994)

Also known as refractory ceramic fibers

Carcinogenicity

Ceramic fibers of respirable size are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to ceramic fibers by inhalation caused benign or malignant lung tumors in rats of unspecified sex (IARC 1988). Since ceramic fibers (respirable size) were listed in the *Seventh Annual Report on Carcinogens,* additional studies in rodents have been identified. The induction of benign and malignant lung tumors following inhalation of ceramic fibers was confirmed in rats (adenoma, carcinoma, and histiocytoma) and also observed in hamsters (adenoma and carcinoma). In addition, mesothelioma of the pleural membrane was observed following exposure by inhalation in rats and male hamsters (Hesterberg *et al.* 1993, Rossiter and Chase 1995, McConnell *et al.* 1996, IARC 2002) and intrapleural injection in rats, and fibrosarcoma or mesothelioma of the peritoneum was observed following exposure by inhalation in rats and intraperitoneal injection in female hamsters and rats of both sexes (IARC 2002).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to respirable ceramic fibers. Since ceramic fibers (respirable size) were listed in the *Seventh Annual Report on Carcinogens,* additional epidemiological studies have been identified. The International Agency for Research on Cancer (IARC 2002) concluded that the data available did not permit evaluation of the carcinogenicity of refractory ceramic fibers in humans, because the studies (Chiazze *et al.* 1997, Walker *et al.* 2002) were either preliminary or limited by small numbers. Since the IARC evaluation, a study of two refractory ceramic fiber manufacturing plants reported a significant threefold excess of urinary cancer (mainly urinary-bladder cancer) based on five deaths, but no excesses of lung cancer or mesothelioma (LeMasters *et al.* 2003).

Properties

Ceramic fibers comprise a wide range of amorphous or crystalline synthetic mineral fibers characterized by their refractory properties (i.e., stability at high temperatures) (IARC 1988). They typically are made of alumina, silica, and other metal oxides or, less commonly, of nonoxide materials such as silicon carbide. Most ceramic fibers are composed of alumina and silica in an approximate 50/50 mixture. By definition, monoxide ceramics, such as alumina and zirconia, are composed of at least 80% of one oxide; they generally contain 90% or more of the base oxide, and specialty products may contain virtually 100%. Nonoxide specialty ceramic fibers, such as silicon carbide, silicon nitride, and boron nitride, also have been produced. Because there are several types of ceramic fibers, such fibers exhibit a range of chemical and physical properties. Most ceramic fibers are white to cream in color and tend to be polycrystallines or polycrystalline metal oxides.

Use

Ceramic fibers are used as insulation materials, because of their ability to withstand high temperatures, and are used primarily for lining furnaces and kilns (IARC 1988, 2002). The products are in the form of blankets, boards, felts, bulk fibers, vacuum-formed or cast shapes, paper, and textiles. Their light weight, thermal-shock resistance, and strength make them useful in a number of industries. High-temperature resistant ceramic blankets and boards are used in shipbuilding as insulation to prevent the spread of fires and for general heat containment. Blankets, rigid boards, and semirigid boards can be applied to the compartment walls and ceilings of ships for this purpose. Ceramic blankets are used as insulation for catalytic converters in the automobile industry and in aircraft and space-vehicle engines. In the metal industry, ceramic blankets are used as insulation on the interior of furnaces. Boards are used in combination with blankets for insulation of furnaces designed to produce temperatures up to about 1,400°C. Ceramic boards are also used as furnace and kiln backup insulation, thermal covering for stationary steam generators, linings for ladles designed to carry molten metal, and cover insulation for magnesium cells and high-temperature reactors in the chemical-process industry. Ceramic textile products, such as yarns and fabrics, are used extensively in such end products as heat-resistant clothing, flame curtains for furnace openings, thermocoupling and electrical insulation, gasket and wrapping insulation, coverings for induction-heating furnace coils, cable and wire insulation for braided sleeving, infrared radiation diffusers, insulation for fuel lines, and high-pressure portable flange covers. Ceramic fibers coated with Teflon are used as sewing threads for manufacturing high-temperature insulation shapes for aircraft and space vehicles. The spaces between the rigid tiles on space shuttles are packed with this fiber in tape form. Ceramic fibers are also used for space-shuttle tiles and other heat shields in the aerospace industry (NIOSH 2006).

Ceramic fibers have consumer applications in the automotive industry, commercial and domestic appliances, commercial fire protection, and hobby furnaces. In the automotive industry, papers and felts containing ceramic fibers are used in catalytic converters, heat shields, air bags, brake pads, clutch facings, and shoulder-belt controls. Commercial and domestic appliances using ceramic-fiber insulation include pizza-oven and deep-fryer heat shields, toasters, self-cleaning ovens, wood stoves, home-heating furnaces, gas hot-water heaters, and simulated fireplace logs. In commercial fire protection, ceramic fibers are used in grease-duct insulation and penetration and expansion-joint seals. They are also used in hobby furnaces, such as ceramic pottery and glass-enameling kilns and blacksmith forges (Venturin *et al.* 1997, NIOSH 2006).

Production

Ceramic fibers are produced by blowing and spinning, colloidal evaporation, continuous filamentation, and, to a lesser extent, whisker-making technologies (vapor-phase deposition used mainly for special applications). Although production of ceramic fibers began in the 1940s, they were not used commercially until the early 1970s (IARC 1988). Worldwide production of ceramic fibers in the early to mid 1980s was estimated at 154 million to 176 million pounds, with U.S. production accounting for about half. U.S. production was estimated at 85.7 million pounds in 1990 and 107.7 million pounds in 1997 (NIOSH 2006). In 2004, U.S. production by four major producers

had fallen to 80 million pounds, accounting for 1% to 2% of worldwide production.

Exposure

The routes of potential human exposure to ceramic fibers include ingestion and dermal contact; however, the primary route of exposure is inhalation during their manufacture, processing, and end use. Manufactured mineral-fiber products release airborne respirable fibers during their production and use. The upper-diameter limit for respirable fibers is considered to be 3 or 3.5 μm. In three refractory ceramic fiber manufacturing facilities, about 90% of airborne fibers were determined to be respirable (< 3 μm in diameter), and about 95% were less than 50 μm long (NIOSH 2006). It was estimated that 31,500 workers potentially were exposed to refractory ceramic fibers during their manufacture, processing, and end use, of whom only about 800 were involved in the manufacturing process (Rice *et al.* 2005).

In the U.S. manufacturing sector, the workplace time-weighted average (TWA) air concentration of refractory ceramic fibers was 10 fibers/cm^3 in the 1950s, decreasing to 0.05 to 2.6 fibers/cm^3 by the 1970s. Concentrations in the 1980s ranged from the level of detection to 0.66 fibers/cm^3. Average TWA exposures were 0.31 fibers/cm^3 between 1993 and 1998 and 0.2 fibers/cm^3 between 2002 and 2006. End users were exposed to refractory ceramic fibers at higher concentrations than were manufacturing workers; average air concentrations for end users were 0.56 fibers/cm^3 between 1993 and 1998 and 0.1 fibers/cm^3 between 2001 and 2005. TWA air concentrations were highest for workers engaged in removal of refractory ceramic fibers, averaging 1.92 fibers/cm^3 between 1993 and 1998, but decreasing to 1.27 fibers/cm^3 between 2001 and 2005. Starting in 2002, respirator use was required during the removal process; between 2002 and 2006, the average TWA concentration adjusted for respirator protection was 0.28 fibers/cm^3, much lower than the measured ambient concentration. The respirator-use rate was low for job categories with lower measured ambient concentrations of refractory ceramic fibers and higher in workplaces with high ambient concentrations (NIOSH 2006, Maxim *et al.* 2008). A study conducted among Ontario construction workers found that 40% of the measured ambient exposure concentrations exceeded the American Conference of Governmental Industrial Hygienists threshold limit value–TWA recommended concentration of 0.2 fibers/cm^3, indicating the need for additional controls, such as adequate ventilation and the use of respirators (Verma *et al.* 2004).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Fine mineral fibers are listed as a hazardous air pollutant.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 15 mg/m^3 total fibers; = 5 mg/m^3 respirable fibers (based on the standard for particulates not otherwise regulated).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 respirable fibers/cm^3 for refractory ceramic fibers.

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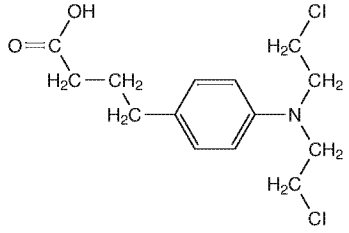
Chlorambucil

CAS No. 305-03-3

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 4-[*p*-[bis(2-chloroethyl)amino]phenyl]butyric acid



Carcinogenicity

Chlorambucil is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have linked treatment with chlorambucil, either alone or in combination with other therapies, with development of cancer, primarily acute nonlymphocytic leukemia, in patients who were treated for other types of cancer or other (nonmalignant) diseases. In addition, a few small epidemiological studies found excesses of cancer in patients treated with chlorambucil. In a randomized clinical trial with 431 polycythemia vera patients, the incidence of acute nonlymphocytic leukemia was 13-fold higher in patients treated with chlorambucil plus phlebotomy than in patients treated with phlebotomy alone, and the risk of leukemia increased with increasing dose and duration of treatment (IARC 1981, 1987).

Cancer Studies in Experimental Animals

Chlorambucil administered by intraperitoneal injection caused tumors of the hematopoietic system in mice of both sexes (lympho-

sarcoma) and in male rats (lymphosarcoma, myelogenous leukemia, and reticulum-cell sarcoma). In mice, it also caused lung tumors in both sexes and ovarian tumors in females. In an initiation-promotion study, chlorambucil acted as a skin-tumor initiator when croton oil was used as the promoter (IARC 1981, 1987). The Internatioal Agency for Research on Cancer (IARC 1987) concluded that there was sufficient evidence for the carcinogenicity of chlorambucil in experimental animals.

Properties

Chlorambucil is a nitrogen mustard that acts as a bifunctional alkylating agent and is used as a pharmaceutical agent (IARC 1987). It exists at room temperature as an off-white granular powder with a slight odor. It is soluble in ethanol, chloroform, ethyl acetate, benzene, and ether, and readily soluble in acid or alkaline solutions. In water, the free acid is insoluble, but the sodium salt is soluble. Chlorambucil is sensitive to oxidation and moisture (IARC 1981). Physical and chemical properties of chlorambucil are listed in the following table.

Property	Information
Molecular weight	304.2[a]
Melting point	64°C to 66°C[a]
Log K_{ow}	1.47 at pH 7.4[a]
Water solubility	12.4 g/L at 25°C[b]
Vapor pressure	5.7×10^{-8} mm Hg at 25°C[a]
Dissociation constant (pK_a)	5.75[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Chlorambucil is used primarily as an antineoplastic agent to treat cancer of the blood and lymphatic system, such as Hodgkin's and non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and primary (Waldenström's) macroglobulinemia. It is also used as a chemotherapeutic agent for Kaposi's disease and cancer of the breast, lung, cervix, ovary, and testis. Chlorambucil is an immunosuppressive agent that has been used to treat rheumatoid arthritis, systemic lupus erythematosus, acute and chronic glomerular nephritis, nephrotic syndrome, psoriasis, Wegener's granulomatosis, chronic active hepatitis, and cold agglutinin disease (IARC 1981). It is also used in veterinary medicine to treat cancer and immune-mediated diseases, including lymphocytic leukemia, multiple myeloma, ovarian cancer, lymphoma, polycythemia rubra vera, pemphigus diseases, eosinophilic granuloma complex, inflammatory bowel disease, feline infectious peritonitis, immune-mediated hemolytic anemia, and immune-mediated platelet destruction (Brooks 2009).

Production

All of the chlorambucil used in the United States is imported from the United Kingdom (HSDB 2009). However, the drug has been formulated in the United States since 1957. Annual U.S. sales of chlorambucil in the mid 1970s were estimated at less than 20 kg (44 lb) (IARC 1975). In 2009, chlorambucil was available from six U.S. suppliers (ChemSources 2009), and one product approved by the U.S. Food and Drug Administration contained chlorambucil as the active ingredient (FDA 2009). Annual U.S. imports of chlorambucil were 32 to 34 kg (71 to 75 lb) in the early 1970s, increasing slightly to 48 kg (106 lb) in 1978 (IARC 1981, HSDB 2009).

Exposure

The primary routes of potential human exposure to chlorambucil are ingestion, inhalation, and dermal contact. Continuous and intermittent oral-treatment schedules are employed for patients treated with chlorambucil. Chlorambucil is available in 2-mg tablets. The initial daily dose is 0.1 to 0.2 mg/kg of body weight (for a total daily dose of 4 to 10 mg) for 3 to 6 weeks. If clinical improvement or bone-marrow toxicity occurs, the dose is reduced. A daily maintenance dose of 2 mg may be required (IARC 1981, FDA 2009). Occupational exposure to chlorambucil may occur through dermal contact or inhalation of dust during formulation, packaging, and administration of the drug product. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 3,719 workers, including 2,018 women, potentially were exposed to chlorambucil (NIOSH 1990). No more recent estimates of exposure were found.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of chlorambucil = U035.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Chlorambucil is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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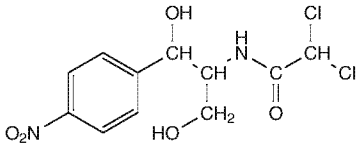
Chloramphenicol

CAS No. 56-75-7

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Chloramphenicol is *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have shown leukemia to occur after medical treatment for chloramphenicol-induced aplastic anemia, and three case reports have documented the occurrence of leukemia after chloramphenicol therapy in the absence of intervening aplastic anemia (IARC 1990). A case-control study in China found an increased risk of leukemia in children who had been treated with chloramphenicol; the risk increased significantly with increasing number of days the drug was taken (Shu *et al.* 1987, 1988). Two case-control studies found large but statistically nonsignificant increases in the risk of aplastic anemia associated with use of chloramphenicol in the six months before the onset of aplastic anemia (Issaragrisil *et al.* 1997, Laporte *et al.* 1998). However, two other case-control studies found no association between the use of chloramphenicol and the risk of leukemia in adults, suggesting that children may be a particularly susceptible subgroup (Zheng *et al.* 1993, Doody *et al.* 1996). One case-control study found an association between chloramphenicol use and increased risk of soft-tissue sarcoma (Zahm *et al.* 1989). Considered together, the many case reports implicating chloramphenicol as a cause of aplastic anemia, the evidence of a link between aplastic anemia and leukemia, and the increased risk of leukemia found in some case-control studies support the conclusion that chloramphenicol exposure is associated with an increased risk of cancer in humans.

Studies on Mechanisms of Carcinogenesis

Chloramphenicol inhibits protein synthesis in the mitochondria of mammalian cells (by binding to ribosomes), which accounts for the sensitivity of proliferating tissues, such as those that promote the formation of blood cells, to its toxicity. Anemia, including aplastic anemia, is a recognized hazard associated with chloramphenicol treatment in humans. In genotoxicity studies, chloramphenicol gave mainly negative results in bacterial systems and mixed results in mammalian systems. The most consistently positive results were observed for cytogenetic effects in mammalian cells, including DNA single-strand breaks and increased frequencies of sister chromatid exchange and chromosomal aberrations. Overall, chloramphenicol appears to be genotoxic (NTP 2000). Several studies have suggested that dehydrochloramphenicol, a chloramphenicol metabolite produced by intestinal bacteria, may be responsible for DNA damage and carcinogenicity (Isildar *et al.* 1988a,b, Jimenez *et al.* 1990, Kitamura *et al.* 1997). This metabolite can undergo nitroreduction in the bone marrow and has been shown to cause DNA single-strand breaks in bone-marrow cells. Mitochondrial abnormalities caused by chloramphenicol are similar to those observed in preleukemia, suggesting that mitochondrial DNA is involved in the pathogenesis of secondary leukemia.

Cancer Studies in Experimental Animals

No adequate studies of the carcinogenicity of chloramphenicol in experimental animals were identified. In male mice given chloramphenicol by intraperitoneal injection in combination with busulfan (the known human carcinogen 1,4-butanediol dimethanesulfonate), the incidence of lymphoma was significantly higher than in mice receiving either busulfan or chloramphenicol alone (Robin *et al.* 1981).

Properties

Chloramphenicol is a naturally occurring antibiotic derivative of dichloroacetic acid that is a white to grayish or yellowish-white fine crystalline powder at room temperature. It is soluble in water and very soluble in methanol, ethanol, butanol, ethyl acetate, chloroform, and acetone. It is fairly soluble in ether, but insoluble in benzene, petroleum ether, and vegetable oils (IARC 1990, HSDB 2009). It is stable under normal shipping and handling conditions (Akron 2009). The biologically active form of chloramphenicol is levorotatory (Chambers 2001). Physical and chemical properties of chloramphenicol are listed in the following table.

Property	Information
Molecular weight	323.1
Melting point	150°C to 152°C
Log K_{ow}	1.14
Water solubility	25 g/L at 25°C
Vapor pressure	1.7×10^{-12} mm Hg at 25°C

Source: HSDB 2009.

Use

Chloramphenicol is an antimicrobial agent with restricted use, because it causes blood abnormalities. It is used to combat serious infections for which other antibiotics are either ineffective or contraindicated. It can be used against gram-positive cocci and bacilli and gram-negative aerobic and anaerobic bacteria (Burnham *et al.* 2000). Chloramphenicol has been used since the 1950s to combat a wide range of microbial infections, including typhoid fever, meningitis, and certain infections of the central nervous system (IARC 1990). It currently is used in eye ointments and drops to treat superficial ocular infections involving the conjunctiva or cornea, in topical ointments or drops to treat the external ear or skin, in tablets for oral administration, and in intravenous suspensions to treat internal infections (FDA 2009, MedlinePlus 2009). Chloramphenicol has also been used in veterinary medicine as a highly effective and well-tolerated broad-spectrum antibiotic. Because of its tendency to cause blood abnormalities in humans, the U.S. Food and Drug Administration in 1997 banned its use in food-producing animals. Chloramphenicol continues to be used to treat both systemic and local infections in cats, dogs, and horses (FDA 1997, Brooks 2008).

Production

Chloramphenicol is produced naturally by the bacterium *Streptomyces venezuelae*. It may be produced by chemical synthesis followed by a step to isolate stereoisomers. A fermentation process also has been described that does not require separation of stereoisomers (IARC 1990). Chloramphenicol was first produced in the United States in 1948 (IARC 1990). Annual U.S. production was estimated to exceed 908 kg (2,000 lb) in 1977 and 1979 (HSDB 2009). In 2009, chloramphenicol was produced by 16 manufacturers worldwide, including 11 in India, 1 in China, 2 in East Asia, and 2 in Europe (SRI 2009). U.S.

imports of chloramphenicol were estimated at 8,150 kg (17,970 lb) in 1977 and 8,200 kg (18,080 lb) in 1979 (HSDB 2009). Since 1989, annual imports of chloramphenicol and its derivatives have remained at or below 16,000 kg (35,000 lb), averaging 8,000 kg (18,000 lb) from 1989 to 2004. Over the same period, annual U.S. exports of chloramphenicol were less than 53,000 kg (117,000 lb) except in 1993, when 1.9 million kilograms (4 million pounds) were exported. No exports were reported for 1998 or 2000 (USITC 2009). In 2002, less than 10,000 lb of chloramphenicol (U.S. production plus imports) was reported under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule; no inventory update reports for chloramphenicol were filed before 2002 (EPA 2004).

Exposure

The primary routes of human exposure to chloramphenicol are oral and dermal, through its use as a drug. Exposure also may occur through inhalation, dermal contact, ingestion, or contact with contaminated water or soil (HSDB 2009). For adults, a typical dosage of chloramphenicol is 50 to 100 mg/kg of body weight per day, divided into four oral or intravenous doses (MedlinePlus 2009). Chloramphenicol also is used in ophthalmic ointments, solutions, and drops. It usually is taken for two to five days or until the infection is diminished. For many infections, continued treatment with chloramphenicol after the infection has resolved is suggested, for periods ranging from 48 hours for eye infections to 8 to 10 days for typhoid fever. No information was found on the number of prescriptions currently written for chloramphenicol in the United States. Children, especially newborns and young infants, metabolize chloramphenicol much more slowly than do adults. Pediatric doses must be lower so as to avoid gray-baby syndrome; this syndrome is characterized by cardiovascular collapse in infants, apparently caused by accumulation of active, unconjugated chloramphenicol in the serum, resulting from low inactivation through glucuronide conjugation in the liver (Chambers 2001). Initial dosages are 25 mg/kg of body weight every 24 hours for infants under one week old, 25 mg/kg every 12 hours for infants aged one to four weeks, and 50 mg/kg every 6 hours for children weighing less than about 25 kg (55 lb) (Sills and Boenning 1999).

Chloramphenicol can be detected in blood serum, plasma, cerebrospinal fluid, and urine. It is rapidly absorbed from the gastrointestinal tract and is distributed extensively through the human body, regardless of administration route. It has been found in the heart, lung, kidney, liver, spleen, pleural fluid, seminal fluid, ascitic fluid, and saliva. Upon metabolism, chloramphenicol yields D-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and chloramphenicol-β-D-glucuronide (IARC 1990). Following degradation of chloramphenicol by intestinal bacteria via amidolysis, 18 metabolites were observed, the major ones being 2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and its *p*-aminophenyl reduction by-product (HSDB 2009). Approximately 90% of chloramphenicol is excreted in urine, mostly as metabolites, including conjugated derivatives; only 15% is excreted as the parent compound (IARC 1990). The half-life of chloramphenicol in adult humans ranges from 1.6 to 4.6 hours. Peak levels appear two to three hours after oral administration of chloramphenicol. In adults given eight 1-g doses, once every six hours, the average peak serum level was 11.2 μg/mL one hour after the first dose and 18.4 μg/mL after the fifth dose. Mean serum levels ranged from 8 to 14 μg/mL over the 48-hour period (Burnham *et al.* 2000). In infants, chloramphenicol's half-life is much longer, ranging from 10 to more than 48 hours in infants aged one to eight days and from 5 to 16 hours in infants aged eleven days to eight weeks (IARC 1990).

Chloramphenicol is released to the environment and may be found in various waste streams as a result of its use as a medicinal and research antimicrobial agent. Chloramphenicol may also be isolated from *S. venezuelae* in the soil (HSDB 2009). If released to air, chloramphenicol will exist primarily as an aerosol and will be removed mainly through dry deposition. Chloramphenicol in the atmosphere reacts with photochemically produced hydroxyl radicals, with a half-life of 12 hours. If released to water, chloramphenicol will be essentially nonvolatile. Adsorption to sediment and bioconcentration in aquatic organisms are not expected to be important processes. If released to soil, chloramphenicol is expected to have high mobility. It is not expected to evaporate from either dry or wet soils. Various studies indicate that chloramphenicol may biodegrade in soil and water. It was found to degrade in adapted activated waste sludge (HSDB 2009).

Occupational exposure during the manufacture of chloramphenicol may occur through inhalation, dermal contact, or ingestion (HSDB 2009). Medical and veterinary personnel who administer drugs containing chloramphenicol also may be exposed (Burnham *et al.* 2000, Brooks 2008).

Regulations

Food and Drug Administration (FDA)

Chloramphenicol is a prescription drug subject to specific labeling requirements.
Extra-label use of chloramphenicol in food-producing animals is prohibited.
Chloramphenicol in ophthalmic and topical dosage form and in tablet form must not be used in animals producing meat, eggs, or milk.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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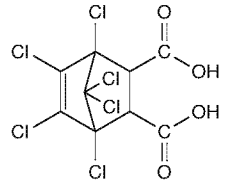
Chlorendic Acid

CAS No. 115-28-6

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)



Carcinogenicity

Chlorendic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chlorendic acid caused tumors in two rodent species and at several different tissue sites. Dietary administration of chlorendic acid caused liver cancer (hepatocellular carcinoma) in female rats and male mice (NTP 1987). In male rats, it caused benign tumors of the liver (adenoma) and pancreas (acinar-cell adenoma); benign lung tumors (alveolar/bronchiolar adenoma) and malignant preputial-gland tumors (carcinoma) may also have been exposure-related.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chlorendic acid.

Properties

Chlorendic acid is structurally related to chlorinated insecticides such as heptachlor, chlordane, endosulfan, endrin, and dieldrin (NTP 1987). It is a white crystalline solid at room temperature. It is slightly soluble in water and in nonpolar organic solvents, but it is readily soluble in methanol, ethanol, and acetone. It emits chlorine when heated to decomposition (IARC 1990). Physical and chemical properties of chlorendic acid are listed in the following table.

Property	Information
Molecular weight	388.8[a]
Melting point	208°C to 210°C[a]
Log K_{ow}	2.3[a]
Water solubility	3.5 g/L at 25°C[b]
Vapor pressure	1.4×10^{-8} mm Hg at 25°C[a]
Dissociation constant (pK_a)	3.1[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Chlorendic acid is used as a flame retardant in polyurethane foams, resins, plasticizers, coatings, epoxy resins, and wool fabrics; in the manufacture of alkyl resins for special paints and inks; in the manufacture of polyester resins with special applications in electrical systems, paneling, engineering plastics, and paint; and in the manufacture of corrosion-resistant tanks, piping, and scrubbers. Chlorendic acid is also used as an extreme-pressure lubricant (NTP 1987, IARC 1990, IPCS 1996, HSDB 2009).

Production

In 1981, U.S. production of chlorendic acid was estimated at 7 million pounds, and imports were about 140,000 lb (NTP 1987). Reported worldwide production of chlorendic acid and anhydride totaled 2 million kilograms (4.4 million pounds) in 1987 (IARC 1990) and 4 million kilograms (8.8 million pounds) in 1996 (IPCS 1996). In 2009, chlorendic acid was produced by two manufacturers in Europe (SRI 2009) and was available from eleven suppliers worldwide, including five U.S. suppliers (ChemSources 2009). No recent reports of U.S. imports or exports specifically of chlorendic acid were found. Reports filed in 1986, 1990, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of chlorendic acid totaled 500,000 lb to 10 million pounds (EPA 2004).

Exposure

The primary route of potential human exposure to chlorendic acid is dermal contact, but inhalation exposure also is possible (HSDB 2009). EPA's Toxics Release Inventory reported annual releases of less than 60 lb to the air from 1995 to 2001; however, one facility reported releases of 420 lb to an off-site hazardous waste landfill and 5 lb to the air in 2002. No releases of chlorendic acid were reported from 2003 to 2006 (TRI 2009). In 2007, 96 lb was released, including 88 lb to off-site management and 8 lb as fugitive air emissions. Releases to the environment can occur from sources other than the direct release of chlorendic acid (IPCS 1996). Chlorendic acid can be released as a result of hydrolytic degradation of polyesters, and it is an oxidation product of numerous pesticides, including endosulfan, chlordane, heptachlor, aldrin, dieldrin, isodrin, and endrin and their metabolites. If released to air, it is expected to exist as a particulate (HSDB 2009). It is subject to photolysis on solid surfaces and in solution, resulting in dechlorination, with a half-life of 16 days on solid surfaces and 5 days in solution (IPCS 1996, HSDB 2009). Chlorendic acid is not expected to volatilize from water or soil; it has a low potential for binding to soil and sediment and is expected to have high mobility in soil. Chlorendic acid has been found in the leachate from landfills at concentrations of up to 455 mg/L and has been identified in at least one hazardous-waste site on the National Priorities List (NTP 1987, IPCS 1996).

Chlorendic acid is manufactured in an essentially closed system, which minimizes potential occupational exposure during the manu-

facturing process (NTP 1987); however, releases may occur from its use (IPCS 1996). When used as a reactive flame-retardant or hardening agent, chlorendic acid bonds covalently to the polymer, reducing the potential for human exposure. Human exposure may also occur through its use as an extreme-pressure lubricant and a chemical intermediate. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 55 workers (classified as Machinery Workers, Except Electrical), including 29 women, potentially were exposed to chlorendic acid (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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Chlorinated Paraffins (C_{12}, 60% Chlorine)

CAS No. 108171-26-2

Reasonably anticipated to be human carcinogens

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Carcinogenicity

Chlorinated paraffins (C_{12}, 60% chlorine) are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chlorinated paraffins (C_{12}, 60% chlorine) caused tumors at several different tissue sites in mice and rats. Administration of chlorinated paraffins by stomach tube increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice of both sexes, the thyroid gland (follicular-cell adenoma and carcinoma) in female mice and rats, and the kidney (tubular-cell adenoma and carcinoma) in male rats. It also caused benign liver tumors (hepatocellular adenoma) in rats of both sexes and possibly mononuclear-cell leukemia in male rats (NTP 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chlorinated paraffins (C_{12}, 60% chlorine). Since chlorinated paraffins were listed in the *Fifth Annual Report on Carcinogens,* a registry-based case-control study of cancer of the liver and biliary tract in autoworkers has been identified (Bardin *et al.* 2005). The case-control study was nested in a cohort study of autoworkers exposed to metalworking fluids. Exposure to specific metalworking fluid components and additives was evaluated, and any exposure to chlorinated paraffins (type not specified) was associated with elevated risk of biliary-tract cancer, based on a small number of cases. No increased risk was found for liver cancer; however, the study included only one exposed worker with liver cancer.

Properties

Chlorinated paraffins are chlorinated long-chain aliphatic compounds. They exist as light-yellow to amber-colored viscous, oily liquids that are usually odorless. The commercial products are complex mixtures that contain paraffins with various carbon-chain lengths and varying chlorine content. The commercial products normally contain stabilizers to inhibit decomposition and may contain isoparaffins (< 1%), aromatic compounds (< 0.1%), and metals as contaminants. Chlorinated paraffins are practically insoluble in water, but many products may be emulsified with water. They are miscible with benzene, chloroform, ether, and carbon tetrachloride, slightly soluble in alcohol, and soluble in most aromatic, aliphatic, and terpene hydrocarbons, ketones, esters, and vegetable and animal oils. Chlorinated paraffins have low volatility and are nonflammable. When heated to decomposition, they emit toxic fumes of hydrochloric acid and other chlorinated compounds. The physical and chemical properties of these chemical mixtures are variable. The octanol-water partition coefficient (log K_{ow}) ranges from 4.48 to 7.38 (IPCS 1996, HSDB 2009).

Use

Chlorinated paraffins are used as extreme-pressure-lubricant additives in metalworking fluids; as flame retardants in plastics, rubber, and paints; to improve water resistance of paints and fabrics; and as a secondary plasticizer in polyvinyl chloride. Small amounts are also used in caulks, sealants, adhesives, detergents, inks, finished leather, and other miscellaneous products, and are allowed as an indirect food additive (NTP 1986, CMR 2002, HSDB 2009, FDA 2010). In the United States, about 50% of chlorinated paraffins are used in metalworking fluids, 20% in plastics additives, 12% in rubber, 9% in coatings, 6% in adhesives, caulks, and sealants, and the remaining 3% for miscellaneous purposes (CMR 2002). Chlorinated paraffins have replaced polychlorinated biphenyls as fire-retardant lubricants (NTP 1986). Between 1914 and 1918, large amounts of chlorinated paraffins were used as solvents for dichloramine-T in antiseptic nasal and throat sprays (IPCS 1996).

Production

Commercial production of chlorinated paraffins for use as additives in extreme-pressure lubricants began in the 1930s. Global production reached 250,000 metric tons (over 550 million pounds) in 1978 but declined to 99 million pounds in 1983. In 2002, the two U.S. manufacturers reported an annual production capacity of 140 million pounds. Demand for chlorinated paraffins remained relatively steady from 1983 to 2009, at 96 million to 100 million pounds (NTP 1986, IARC 1990, CMR 2002). In 2009, chlorinated paraffins were produced by 78 manufacturers worldwide, including 2 in the United States, 40 in

China, and 22 in India (SRI 2009). No specific data on U.S. imports or exports of chlorinated paraffins were found.

Exposure

No information on potential human exposure specifically to chlorinated paraffins (C_{12}, 60% chlorine) was found, but information was available on potential human exposure to the class of chlorinated paraffins. The routes of potential human exposure include inhalation, dermal contact, and ingestion, primarily through contamination of foods (IPCS 1996). Because chlorinated paraffins are permitted in adhesives used in food packaging, the general population could be exposed to very low concentrations through ingestion of contaminated food products wrapped in these materials (FDA 2010). Short-chain chlorinated paraffins (SCCPs) (C_{10} to C_{13}) have also been found in food products contaminated through environmental exposure. In Japan, SCCPs were found in high-lipid-content foods such as dairy products, vegetable oil, salad dressing, and mayonnaise, at a mean concentration of 140 ng/g of wet weight (Bayen *et al.* 2006). The next-most-contaminated Japanese food category was fish and shellfish, with SCCP concentrations of 16 to 18 ng/g of wet weight. The levels in Japanese foods would translate to an average daily intake of 680 ng/kg of body weight for a 1-year-old female infant in Japan (the highest rate reported). In European butter samples, SCCPs were measured at concentrations of 1.2 to 2.7 µg/kg of lipid content. In addition, chlorinated paraffins have been isolated from human tissues, including liver, kidney, and adipose tissue, at concentrations of up to 1.5 mg/kg of wet tissue (most values were < 0.09 mg/kg) (Campbell and McConnell 1980), and from breast milk at concentrations up to 0.8 mg/kg of milk fat (Thomas *et al.* 2006).

Chlorinated paraffins are lipophilic and persistent in the environment. The very low vapor pressure indicates that these compounds will not volatilize easily. If released to air, they will exist as particulates and will not remain in the atmosphere; they may be photochemically degraded, with a half-life of 1.2 to 1.8 days (IPCS 1996). Chlorinated paraffins have been measured in the atmosphere in the United Kingdom at concentrations of up to 3.4 ng/m^3 (Barber *et al.* 2005).

Chlorinated paraffins have low water solubility and a high log K_{ow}. Therefore, if released to water, they will not volatilize from water or remain in solution, but will adsorb to sediment or suspended solid material. If released to soil, chlorinated paraffins are bound to the soil particles and are not expected to volatilize or to leach into groundwater. Based on limited data, chlorinated paraffins do not biodegrade readily (IPCS 1996, HSDB 2009). In 1988, chlorinated paraffins were measured in the United States in water, sediment, and aquatic organisms downstream from industrial facilities where chlorinated paraffins were made or used. The concentrations measured were less than 8 µg/L in water (compared with < 0.3 µg/L upstream from the same facility) and up to 40 mg/kg in sediment. SCCP concentrations measured in Lake Ontario sediment cores in 1998 averaged 49 µg/kg. Maximum SCCP concentrations in the sediment cores increased from less than 50 µg/kg in 1900 to over 800 µg/kg in the 1980s and then declined to 410 µg/kg in 1998 (Marvin *et al.* 2003). These data are consistent with a maximum concentration of 347 µg/kg in sediment samples collected in the Czech Republic in 2003 (Pribylova *et al.* 2006). In 1980, short- and medium-chain chlorinated paraffins were measured in non-industrialized areas of the United Kingdom at concentrations up to 1 µg/L in water and up to 1 mg/kg in sediment; in industrialized areas, measured concentrations in sediment were as high as 15 mg/kg (Campbell and McConnell 1980). Marine samples collected away from land in the North and Baltic Seas from 2001 to 2003 contained SCCPs at concentrations of up to 377 µg/kg (Huttig and Oehme 2005).

Aquatic organisms were found to contain chlorinated paraffins (C_{10} to C_{20}) at concentrations similar to those in sediment; for example, a mean concentration of 3.25 mg/kg was found in mussels collected in the United Kingdom (Campbell and McConnell 1980). Chlorinated paraffins potentially may bioaccumulate in some animal species (IPCS 1996, Huttig and Oehme 2005); however, they do not biomagnify in the food chain (Madeley and Birtley 1980). They were also measured in the blubber of marine mammals at concentrations of 0.164 to 1.4 µg/kg and in the fat of terrestrial wildlife at up to 4.4 mg/kg (IPCS 1996).

Occupational exposure is likely in production plants or in industries using chlorinated paraffins (IPCS 1996). In facilities using metalworking fluids containing chlorinated paraffins for milling, cutting, and grinding, aerosol concentrations of up to 1.15 mg/m^3 were reported; however, it is not known whether chlorinated paraffin aerosols are in the inhalable size range. Dermal exposure of the hands and forearms was predicted to range from 0.1 to 1 mg/cm^2 per day for production of chlorinated paraffins and up to 1.5 mg/cm^2 for their use as metalworking fluids. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 573,193 workers, including 38,354 women, potentially were exposed to substances in the category "Paraffin, chlorinated (CAS 63449-39-8, Paraffin waxes and hydrocarbon waxes)" and that 61,464 workers, including 3,717 women, potentially were exposed to substances in the smaller category of "Chlorinated paraffin" (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Chlorinated paraffins are considered marine pollutants, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA)

Chlorinated paraffins are allowed for use as indirect additives used in food contact substances as prescribed in 21 CFR 175 and 177.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 5 mg/m^3 for paraffin oil mist.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,500 mg/m^3 for paraffin oil mist.
Recommended exposure limit (REL) = 5 mg/m^{3}for paraffin oil mist.
Short-term exposure limit (STEL) = 10 mg/m^3 for paraffin oil mist.

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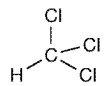
Chloroform

CAS No. 67-66-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Chloroform is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chloroform caused tumors in two rodent species and at two different tissue sites. Administration of chloroform by stomach tube caused liver cancer (hepatocellular carcinoma) in mice of both sexes (NCI 1976) and kidney tumors (epithelial tumors) in male mice and rats (IARC 1979, Roe *et al.* 1979).

Since chloroform was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified, which reported that chloroform caused liver and kidney tumors by additional routes of exposure. Benign liver tumors (adenoma) were observed in female rats administered chloroform in the drinking water (IARC 1987, 1999) and female mice exposed by inhalation (Yamamoto *et al.* 2002). Benign and malignant kidney tumors (tubular-cell adenoma, carcinoma, or adenocarcinoma) were observed in male rats exposed via the drinking water (IARC 1987, 1999), male mice exposed by inhalation (Yamamoto *et al.* 2002), and male rats following combined exposure via inhalation and the drinking water (Nagano *et al.* 2006).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chloroform. Two community-based studies of exposure to chlorinated water found excesses of cancer at several tissue sites, particularly the urinary bladder (Cantor *et al.* 1978, Hogan *et al.* 1979), but a causal relationship could not be inferrred (IARC 1982).

Since chloroform was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified, mostly involving exposure to chlorinated water, which may contain chloroform and other chlorinated hydrocarbons, via drinking, bathing, showering, or swimming. The International Agency for Research on Cancer (IARC 1999) concluded that a causal relationship between cancer and chloroform could not be inferred, because of the use of indirect methods of assessing exposure, incomplete control for confounding by exposure to other water impurities or other risk factors, and differing results for men and women. Overall, cohort and case-control studies found a relationship between exposure to chlorinated water and the risk of some types of cancer, particularly of the urinary bladder and rectum and possibly of the colon (IARC 1982, 1987, 1999).

Since the last IARC review, additional community-based studies have been identified, which have examined cancer risks associated with estimated exposure to chlorinated drinking water. Several studies, including a pooled analysis of six case-control studies, reported associations of urinary-bladder cancer with overall trihalomethane exposure (Villanueva *et al.* 2004, 2007, Chang *et al.* 2007, Michaud *et al.* 2007); two studies found an exposure-response relationship for men but not women (Villanueva *et al.* 2004, 2007). One study also found an association in men between urinary-bladder cancer and exposure to trihalomethanes via bathing, showering, or swimming in pools (Villanueva *el al.* 2007). Some studies also reported associations between colorectal cancer and overall trihalomethane exposure (King *et al.* 2000, Kuo *et al.* 2009, 2010). Few studies of drinking-water exposure attempted to distinguish the risk associated specifically with exposure to chloroform, and none controlled adequately for exposure to other trihalomethanes or other risk factors. However, one study found a significantly elevated risk of urinary-bladder cancer associated with high levels of chloroform in drinking water (Bove *et al.* 2007).

Properties

Chloroform is a trihalomethane that exists at room temperature as a clear, colorless, highly refractive heavy liquid with a pleasant ethereal odor (Akron 2009, HSDB 2009). It is slightly soluble in water, soluble in carbon disulfide, and miscible with alcohol, ether, benzene, carbon tetrachloride, and fixed and volatile oils (HSDB 2009). Chloroform is stable under normal temperatures and pressures in a closed container (Akron 2009). It is light sensitive and may decompose slowly in the presence of sunlight and in the dark in the presence of air (IARC 1979). Physical and chemical properties of chloroform are listed in the following table.

Property	Information
Molecular weight	119.4[a]
Specific gravity	1.4888 at 25°C/25°C[a]
Melting point	–63.41°C[a]
Boiling point	61.2°C[a]
Log K_{ow}	1.97[a]
Water solubility	7.950 g/L at 25°C[b]
Vapor pressure	197 mm Hg at 25°C[a]
Vapor density relative to air	4.12[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

In 2007, about 95% of the chloroform produced in the United States was used to make chlorodifluoromethane (HCFC-22, also known as R-22); 62% of HCFC-22 was used as a refrigerant, and 33% was used in the production of fluoropolymers (HSDB 2009). However, the use of HCFC-22 is being phased out under the 1987 Montreal Protocol, and as of January 1, 2010, manufacturers were not allowed to pro-

duce new air conditioners or heat pumps containing HCFC-22 (EPA 2010). The remaining chloroform produced has miscellaneous uses, including as a solvent or an extraction solvent for lacquers, floor polishes, adhesives in artificial silk manufacturing, resins, fats, greases, gums, waxes, oils, alkaloids, penicillin, vitamins, flavors, and rubber; as a drycleaning spot remover; in fire extinguishers; as an intermediate in the preparation of dyes and pesticides; and as a fumigant for stored grain crops (IARC 1979, ATSDR 1997, HSDB 2009). It may also be used as a local anesthetic in certain dental endodontic surgeries and in aspirin-chloroform mixtures applied topically to relieve pain from severe cases of herpes or post-therapeutic neuralgia (ATSDR 1997, HSDB 2009).

Before 1976, chloroform was used in a wide variety of drug products, including cough syrups, antihistamines, and decongestants (IARC 1979). In the 1970s, the U.S. Food and Drug Administration banned drugs containing chloroform and also banned its use in cosmetics because of its carcinogenicity. However, it did not ban drug products that contain chloroform in residual amounts resulting from its use as a solvent in manufacturing or its presence as a by-product from the synthesis of drug ingredients (IARC 1979, ATSDR 1997). An approved new drug application is required for marketing any drug product containing chloroform (FDA 1999).

Production

One U.S. manufacturer began chloroform production in 1903, but commercial production was not reported until 1922 (IARC 1979). From the early 1980s to the mid 1990s, the annual production of chloroform increased by 20% to 25%, primarily because of the great demand for the refrigerant HCFC-22 (ATSDR 1997). In 2004, annual U.S. production capacity at four manufacturing facilities was 765 million pounds (CMR 2004). In 2009, chloroform was produced by 40 manufacturers worldwide, 4 of which were in the United States (SRI 2009), and was available from 105 suppliers, including 42 U.S. suppliers (ChemSources 2009). U.S. imports of chloroform decreased from a high of 17.3 million kilograms (38 million pounds) in 1989 to a low of 44,000 kg (97,000 lb) in 1997 and have since fluctuated; in 2008, imports totaled 180,000 kg (0.4 million pounds). U.S. exports of chloroform increased from 15 million kilograms (33.5 million pounds) in 1985 to 180 million kilograms (396 million pounds) in 2004 and have since been variable, decreasing to 120 million kilograms (264 million pounds) in 2008 (USITC 2009).

Exposure

The routes of potential human exposure to chloroform are ingestion, inhalation, and dermal contact (HSDB 2009). Exposure to chlorinated water is expected to be a primary source of human exposure to chloroform, because many public water supplies and swimming pools contain trihalomethanes as by-products of chlorination for disinfection purposes. Chloroform is the most prevalent trihalomethane in treated water. Most exposure of the general population occurs during the use of chlorine-treated water (e.g., for showering, swimming, cleaning, drinking, or cooking) (IARC 1979, 1999, ATSDR 1997, HSDB 2009). Chloroform's concentration in water systems is not constant over time or location, because trihalomethane concentrations increase with the length of time the water remains in the distribution system (Ashley *et al.* 2005). Typical daily levels of adult exposure to chloroform from drinking water are estimated to range from 0.199 to 1.89 μg/kg of body weight (WHO 2004). Foods such as dairy products, oils and fats, vegetables, bread, and beverages may also contain small amounts of chloroform (IARC 1999, HSDB 2009), resulting in an estimated average daily intake of 0.043 to 0.478 μg/kg of body weight for adults aged 20 to 59 years (IPCS 2004).

Chloroform is also present in the ambient air, surface water, ground water, and soil. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of chloroform declined steadily from about 28 million pounds in 1988 to 706,555 lb in 2007, when it was released from 67 facilities (TRI 2009). Chloroform has been detected in the atmosphere at concentrations ranging from 0.10 to 10.0 μg/m^3 in urban areas in the United States and in indoor air at 0.17 to 43.9 μg/m^3 (IPCS 2004). It has also been measured in surface water in rivers, lakes, and oceans, and in precipitation. The highest concentration recently measured in a U.S. river was 2.1 μg/L (McCulloch 2003). In open oceans and estuaries, the highest reported concentration was 70 μg/L in the estuary of the Mersey River, in England (Zok *et al.* 1998). Chloroform has also been measured in snowpack in the Antarctic, Italy, and Germany, at a maximum concentration of 380 ng/kg (0.00038 mg/kg) in Antarctic snow (Zoccolillo *et al.* 2007). Contamination of groundwater by chloroform was found at the site of a plutonium processing facility near Knoxville, Tennessee, at a mean concentration of 0.108 mg/L (Datskou and North 1996). Chloroform was measured at 1.1 mg/kg in soil samples taken from a small garden in Spain irrigated with chlorine-treated tap water (Campillo *et al.* 2004).

If exposure to chloroform through inhalation of ambient air and indoor air and through ingestion of food are added to exposure through ingestion of drinking water, daily adult exposure is estimated to range from 0.70 μg/kg to over 3.0 μg/kg of body weight. Exposure due to daily showering (inhalation and dermal) alone is estimated to add 0.36 to 3.4 μg/kg. Two studies reported changes in chloroform concentrations in the blood as a result of household water use, including showering, bathing, and hand washing of dishes (Ashley *et al.* 2005, Nuckols *et al.* 2005). The concentration of chloroform in the blood increased 2- to 7-fold after showering; at two study sites, the median water concentrations of chloroform were 8 and 85 ppb, and the median blood concentrations after showering were 57 and 280 ppt (ng/L) (Nuckols *et al.* 2005). Ingestion of drinking water caused little elevation in blood levels of chloroform; however, the use of hot water during showering, bathing, and hand washing of dishes caused significant peaks in chloroform blood concentrations. Dermal absorption of chloroform is affected by water temperature during bathing. Among 10 subjects, the mean amount of chloroform exhaled was 0.2 μg at the lowest bath-water temperature (30°C) and 7 μg at the highest temperature (40°C), for a 35-fold increase (Gordon *et al.* 1998).

Several studies have shown that inhalation and dermal exposure to chloroform are important during swimming. Lindstrom *et al.* (1997) measured dermal and inhalation exposure to chloroform from swimming in a chlorinated pool; two college students (one male and one female) were monitored during a typical two-hour workout. The mean concentration of chloroform in their breath was as high as 371 μg/m^3 and 339 μg/m^3, over twice the maximum possible concentration from inhalation exposure only. Furthermore, the maximum alveolar breath concentrations ultimately reached over twice the ambient indoor chloroform concentration, suggesting that dermal absorption was more important than inhalation. The dermal contribution was estimated at over 90% of total exposure. Other studies found that inhalation exposure to chloroform resulted in 80% absorption. Placental transfer of chloroform also has been demonstrated (IPCS 2004).

Occupational exposure may occur during the manufacture or use of chloroform (ATSDR 1997). Workers at wastewater and other treatment plants can be exposed to significant levels of chloroform. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 95,772 workers, including 41,394 women,

in 20 industrial categories potentially were exposed to chloroform (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Chloroform is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.
Prevention of Accidental Release: Threshold quantity (TQ) = 20,000 lb.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.
Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 5.7 µg/L; based on fish or shellfish consumption only = 470 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.
Reportable quantity (RQ) = 10 lb.
Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 6.0 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chloroform = U044, F024, F025, K009, K010, K019, K020, K021, K029, K073, K116, K149, K150, K151, K158.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.080 mg/L for the sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform.

Food and Drug Administration (FDA)

All drug products containing chloroform have been removed from the market, and a new drug application is required for approval.
Chloroform may not be used as an ingredient in cosmetic products.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Ceiling concentration = 50 ppm (240 mg/m^3).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Short-term exposure limit (STEL) = 2 ppm (9.78 mg/m^3) (60-min exposure).
Immediately dangerous to life and health (IDLH) limit = 500 ppm.
Listed as a potential occupational carcinogen.

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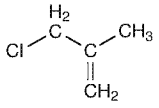
3-Chloro-2-methylpropene

CAS No. 563-47-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as 3-chloro-2-methyl-1-propene



Carcinogenicity

3-Chloro-2-methylpropene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 3-chloro-2-methylpropene caused tumors in two rodent species and at several different tissue sites. Administration of 3-chloro-2-methylpropene by stomach tube caused benign or malignant tumors of the forestomach (squamous-cell papilloma or carcinoma) in mice and rats of both sexes; in mice, some of the malignant tumors metastasized to other organs. Kidney and urinary-bladder tumors in male rats may also have been related to 3-chloro-2-methylpropene exposure.

Since 3-chloro-2-methylpropene was listed in the *Fifth Annual Report on Carcinogens*, an additional study in mice has been identified. Inhalation exposure to 3-chloro-2-methylpropene caused benign forestomach tumors (squamous-cell papilloma) in mice of both sexes and benign Harderian-gland tumors (adenoma) in female mice (Katagiri *et al.* 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 3-chloro-2-methylpropene.

Properties

3-Chloro-2-methylpropene exists at room temperature as a colorless to straw-colored liquid with a sharp, disagreeable odor. It is slightly soluble in water, soluble in acetone, very soluble in chloroform, and miscible with ethanol and diethyl ether. It can polymerize on exposure to light and is explosively flammable. The vapors are heavier than air and may travel from the source and collect in low or confined areas (IARC 1995, Akron 2009, HSDB 2009). Physical and chemical properties of 3-chloro-2-methylpropene are listed in the following table.

Property	Information
Molecular weight	90.6[a]
Specific gravity	0.92 at 20°C/4°C[a]
Melting point	< –80°C[a]
Boiling point	71°C to 72°C[a]
Log K_{ow}	2.48[b]
Water solubility	1.4 g/L at 25°C[b]
Vapor pressure	101.7 mm Hg at 20°C[a]
Vapor density relative to air	3.1[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

3-Chloro-2-methylpropene is used primarily as a chemical intermediate in the production of organic chemicals, including 3-dimethylamino-2-methylpropyl chloride hydrochloride, 2-methylepichlorohydrin, and the pesticides carbofuran, ethalfluralin, and fenbutatin oxide. In 1985, over 97% of its production was used as an intermediate in the production of agricultural chemicals; the remainder was used as a textile or perfume additive or for other purposes. Outside of the United States, 3-chloro-2-methylpropene has been used as an insecticide fumigant for grains, tobacco, and soil; however, it is not registered for use as a pesticide in the United States (NTP 1986, IARC 1995, HSDB 2009).

Production

In 1984, U.S. production of 3-chloro-2-methylpropene was estimated at 12 million to 24 million pounds (NTP 1986). In 2009, 3-chloro-2-methylpropene was produced by one manufacturer worldwide, in China (SRI 2009), and was available from 18 suppliers, including 9 U.S. suppliers (ChemSources 2009). Reports filed in 1986, 1990, 1998, 2002, and 2006 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 3-chloro-2-methylpropene totaled 10 million to 50 million pounds; in 1994, the quantity was 1 million to 10 million pounds (EPA 2004, 2009).

Exposure

The primary routes of potential human exposure to 3-chloro-2-methylpropene are inhalation, ingestion, and dermal contact. Use as a fumigant would result in the direct release of 3-chloro-2-methylpropene to the environment; however, this use has not been reported in the United States (HSDB 2009). Consumers could be exposed through ingestion of food products that had absorbed 3-chloro-2-methylpropene (NTP 1986). According to EPA's Toxics Release Inventory, environmental releases of 3-chloro-2-methylpropene in 1996 and 1997 totaled 26,000 lb. In 2007, one facility released 6,536 lb to air (TRI 2009). If released to air, 3-chloro-2-methylpropene will exist only in the vapor phase and be degraded by reaction with hydroxyl radicals, with an estimated half-life of 10 hours, and with ozone, with an esimated half-life of 27 hours (HSDB 2009). If released to water, 3-chloro-2-methylpropene will volatilize, with an estimated half-life of 3 hours in a model river and 4 days in a model lake. If released to soil, it is expected to volatilize and to have high mobility. It is not expected to bind to soil or sediments. It is expected to biodegrade under aerobic conditions and to have a low potential for bioaccumulation. Around 1980, 3-chloro-2-methylpropene was detected in the ambient air in an industrial area near Curtis Bay, Maryland, at concentrations of up to 400 $\mu g/m^3$ (NTP 1986).

Occupational exposure to 3-chloro-2-methylpropene may occur during its manufacture or use as an intermediate in organic synthesis. No data on occupational exposure were found.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of 3-chloro-2-methylpropene is subject to certain provisions for the control of volatile organic compound emissions.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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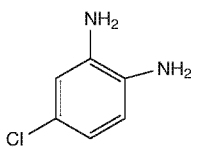
4-Chloro-*o*-phenylenediamine

CAS No. 95-83-0

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

4-Chloro-*o*-phenylenediamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4-chloro-*o*-phenylenediamine caused tumors in two rodent species and at several different tissue sites. Dietary administration of technical-grade 4-chloro-*o*-phenylenediamine caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and benign or malignant tumors of the urinary bladder and forestomach (papilloma or carcinoma) in rats of both sexes (NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4-chloro-*o*-phenylenediamine.

Properties

4-Chloro-*o*-phenylenediamine is a chlorinated aromatic amine that exists as a brown crystalline solid or powder at room temperature (Akron 2009). It is slightly soluble in water, but it is soluble in benzene and very soluble in ethanol and ether. 4-Chloro-*o*-phenylenediamine is stable at normal temperatures and pressures. Physical and chemical properties of 4-chloro-*o*-phenylenediamine are listed in the following table.

Property	Information
Molecular weight	142.6[a]
Melting point	76°C[a]
Boiling point	229°C[b]
Log K_{ow}	1.28[a]
Water solubility	6.6 g/L at 25°C[b]
Vapor pressure	2.06×10^{-3} mm Hg 25°C[b]
Dissociation constant (pK_a)	3.83 at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

4-Chloro-*o*-phenylenediamine can be used as an oxidation base for dye preparation, as a chemical intermediate to produce 5-chlorobenzotriazole, as a curing agent for epoxy resins, as a reagent in gas chromatography, and to synthesize experimental pharmaceuticals. It has been used as a chemical intermediate in dye production and was patented as a hair-dye component, but there is no evidence that it is currently used in the United States for these purposes (IARC 1982, HSDB 2009).

Production

4-Chloro-*o*-phenylenediamine was first produced commercially in the United States in 1941 (IARC 1982). In 2009, 4-chloro-*o*-phenylenediamine was produced by three manufacturers worldwide, including one in India and two in Europe (SRI 2009), and was available from 20 suppliers worldwide, including 9 U.S. suppliers (ChemSources 2009). U.S. production in 1977 was estimated at 1,000 to 10,000 lb (IARC 1982). No data on U.S. imports or exports of 4-chloro-*o*-phenylenediamine were found. Under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule, U.S. production plus imports totaled 10,000 to 500,000 lb in 1986 (EPA 2004); no later inventory update reports were filed.

Exposure

Because of its limited use in consumer products, little exposure of the general population to 4-chloro-*o*-phenylenediamine is expected. Nevertheless, exposure could potentially occur if residues were present in hair dyes or in products made from 5-chlorobenzotriazole (IARC 1982, HSDB 2009). The primary routes of potential human exposure to 4-chloro-*o*-phenylenediamine are ingestion, inhalation, and dermal contact by workers in the dye and chemical industries and those involved in pharmaceutical research (NCI 1978). Exposure could occur during production and use of 4-chloro-*o*-phenylenediamine or following accidental releases. No data were found on the numbers of workers potentially exposed to 4-chloro-*o*-phenylenediamine.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 4-chloro-*o*-phenylenediamine were identified.

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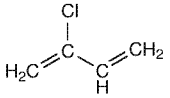
Chloroprene

CAS No. 126-99-8

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Also known as 2-chloro-1,3-butadiene



Carcinogenicity

Chloroprene is *reasonably anticipated to be a human carcinogen* based on evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Inhalation exposure to chloroprene caused tumors at several different tissue sites in mice and rats. It caused lung tumors (alveolar/bronchiolar adenoma and/or carcinoma) in mice of both sexes and in male rats; kidney tumors in rats of both sexes and in male mice (renal-tubule adenoma); and mammary-gland tumors in female rats (fibroadenoma) and mice. In rats of both sexes, it also caused tumors of the oral cavity (squamous-cell papilloma and carcinoma) and thyroid gland (follicular-cell adenoma or carcinoma). In mice, it also caused tumors of the forestomach (squamous-cell papilloma), Harderian gland (adenoma or carcinoma), and blood vessels (hemangioma and hemangiosarcoma) in both sexes and tumors of the liver (hepatocellular adenoma and carcinoma), Zymbal gland (carcinoma), skin (sarcoma), and mesentery (sarcoma) in females (NTP 1998).

Cancer Studies in Humans

Data from two early epidemiological studies suggested that occupational exposure to chloroprene may increase the risks of cancer of the liver, lung, and digestive and lymphohematopoietic systems (Pell 1978, Li *et al.* 1989). Since chloroprene was listed in the *Ninth Report on Carcinogens*, additional epidemiological studies have been identified. Mortality from leukemia and liver cancer was significantly increased among shoe-manufacturing workers, and liver-cancer incidence and mortality were signficantly increased among chloroprene-production workers (Bulbulyan *et al.* 1998, 1999). However, two other cohort studies of chloroprene-production workers found no excess of liver cancer (Colonna and Laydevant 2001, Marsh *et al.* 2007a,b). These two studies reported increased risks of lung or respiratory cancer; however, the risk estimates were not statistically significant or related to exposure category in the small cohort study (Colonna and Laydevant 2001) and were significantly elevated in only one of several plants in the large multi-plant study (Marsh *et al.* (2007a,b).

Studies on Mechanisms of Carcinogenesis

Chloroprene (the 2-chloro analogue of 1,3-butadiene) caused all of the same types of tumors that 1,3-butadiene caused in mice except for lymphoma and tumors of the preputial gland and ovary (NTP 1998).

In vitro metabolism of chloroprene by mouse, rat, hamster, and human microsomes produced (1-chloroethenyl)oxirane, an epoxide that is thought to react with DNA and can be further metabolized by hydrolysis and glutathione conjugation (Himmelstein *et al.* 2001). However, many studies on the genotoxicity of chloroprene have given negative results, and positive results from earlier studies were attributed to differences in the age and purity of the chloroprene samples (Westphal 1994, NTP 1998). The mutagenicity of chloroprene in bacteria (Bartsch *et al.* 1975, 1979) was considered to be due to cyclic dimers that accumulate in aged samples (Westphal *et al.* 1994).

At the same exposure concentrations as used in the inhalation-exposure studies of cancer in mice, chloroprene did not cause sister chromatid exchange or chromosomal aberrations in mouse bone-marrow cells, nor did it increase the frequency of micronucleated erythrocytes in peripheral blood (Tice *et al.* 1988). During another inhalation-exposure study in mice and rats, chloroprene caused dominant lethal mutations in both species and chromosomal aberrations in mouse bone marrow cells (Sanotskii 1976). However, despite the largely negative findings for genotoxicity, chloroprene-induced lung and Harderian-gland tumors from mice had a high frequency of unique mutations of the K-*ras* proto-oncogene (NTP 1998). In addition, occupational-exposure studies reported increased frequencies of chromosomal aberrations in the lymphocytes of workers (IARC 1979).

Properties

Chloroprene is a halogenated alkene that exists at room temperature as a clear colorless liquid with a pungent ether-like odor. It is practically insoluble in water, soluble in alcohol, and miscible with acetone, benzene, and ethyl ether. It is highly flammable and polymerizes on standing, making it unstable in the environment (Akron 2009). Physical and chemical properties of chloroprene are listed in the following table.

Property	Information
Molecular weight	88.5[a]
Specific gravity	0.956 at 20°C/4°C[a]
Melting point	–130°C[a]
Boiling point	59°C[a]
Log K_{ow}	2.53[b]
Water solubility	0.875 g/L at 25°C[b]
Vapor pressure	215 mm Hg at 25°C[a]
Vapor density relative to air	3[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

The only commercial use identified for chloroprene is as a monomer in the production of the elastomer polychloroprene (neoprene), a synthetic rubber used in the production of automotive and mechanical rubber goods, adhesives, caulks, flame-resistant cushioning, construction materials, fabric coatings, fiber binding, and footwear. Other uses of this polymer include applications requiring chemical, oil, or weather resistance or high gum strength. The U.S. Food and

Drug Administration permits the use of chloroprene as a component of adhesives used in food packaging and also permits the use of polychloroprene in products intended for use with food (IARC 1979, 1999, NTP 1998).

Production

In 2009, chloroprene was produced by one manufacturer each in the United States and China and two manufacturers in Europe (SRI 2009) and was available from eleven suppliers, including seven U.S. suppliers (ChemSources 2009). Reports filed between 1986 and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of chloroprene totaled 100 million to 500 million pounds (EPA 2004).

Exposure

The routes of human exposure to chloroprene are inhalation, ingestion, and dermal contact. Chloroprene is not known to occur naturally in the environment (IARC 1999). The main sources of environmental releases are effluent and emissions from facilities that use chloroprene to produce polychloroprene elastomers. According to EPA's Toxics Release Inventory, environmental releases of chloroprene have decreased steadily from a high of over 2 million pounds in 1988 (the year reporting started). In 2007, two facilities reported chloroprene releases of over 275,000 lb, and seven facilities reported releases of 1,300 lb or less, almost all to air (TRI 2009). When released to air, chloroprene reacts with photochemically generated hydroxyl radicals, with a half-life of 18 hours, and smaller amounts are removed by reaction with ozone, with a half-life of 10 days. Based on the Henry's law constant and octanol-water partition coefficient, chloroprene is expected to be removed from water and damp soil primarily by volatilization. If released to water, chloroprene is expected to volatilize from the surface, with a half-life of 3 hours from streams and 4 days from lakes. It will not adsorb to sediment or suspended solids or bioaccumulate in aquatic organisms. If released to soil, chloroprene is expected to volatilize or may leach into groundwater (HSDB 2009). In 1991, EPA's Urban Air Toxics Monitoring Program identified chloroprene in 88 of 349 samples (25.2%), at concentrations ranging from 0.01 to 1.78 ppb (0.036 to 6.44 $\mu g/m^3$). The results were similar in 1996, but in 2000 and 2005, chloroprene was detected in only one sample.

The main source of occupational exposure to chloroprene is the manufacture of chloroprene or polychloroprene (NTP 1998). In 1977, it was estimated that 2,500 to 3,000 workers were exposed to chloroprene during its manufacture and polymerization (Infante 1977). Chloroprene monomer is manufactured in a closed system, which is then used on site to make the polymer. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 17,700 workers, including 650 women, potentially were exposed to chloroprene or polychloroprene (NIOSH 1990). Time-weighted 8-hour average concentrations at three facilities (two in the United States and one in Northern Ireland) from 1975 to 1992 were 1 ppm in all but three samples, and chloroprene concentrations in the monomer manufacturing phase were below 1.8 ppm in all samples (Hall *et al.* 2007). During the polymer manufacturing phase, chloroprene concentrations were as high as 4.66 ppm in Northern Ireland and 3.42 ppm in the United States. By 1992, concentrations in all polymer facilities were lower (1.4 and 0.53 ppm in the United States and 0.37 ppm in Northern Ireland).

Regulations

Department of Transportation (DOT)

Chloroprene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 25 ppm (90 mg/m^3).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm (36 mg/m^3).

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 1 ppm (3.6 mg/m^3) (15-min exposure).
Immediately dangerous to life and health (IDLH) limit = 300 ppm (1,086 mg/m^3).
Listed as a potential occupational carcinogen.

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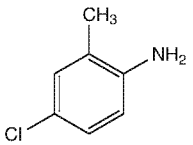
p-Chloro-*o*-toluidine and Its Hydrochloride

CAS Nos. 95-69-2 and 3165-93-3

Reasonably anticipated to be human carcinogens

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 4-chloro-*o*-toluidine or 4-chloro-2-methylaniline



Carcinogenicity

p-Chloro-*o*-toluidine and its hydrochloride salt are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of *p*-chloro-*o*-toluidine from epidemiological studies in humans. Three cohort studies found high relative risks for urinary-bladder cancer among workers exposed to *p*-chloro-*o*-toluidine; however, confounding by co-exposure to other potential urinary-bladder carcinogens could not be ruled out. Documented human exposure to *p*-chloro-*o*-toluidine has occurred primarily in the dye and synthetic-chemical industries (IARC 2000). Between 1982 and 1990, 7 cases of urinary-bladder cancer were detected in a group of 49 German and Danish workers who were involved in producing the insecticide chlordimeform from *p*-chloro-*o*-toluidine on an irregular basis for an average of 18 years (Popp *et al.* 1992). The incidence of urinary-bladder tumors in this group was significantly higher than the expected incidence based on national or regional cancer registries. A brain tumor also occurred in one of the seven workers with urinary-bladder cancer. Exposure levels were not documented, but exposure to *p*-chloro-*o*-toluidine from 1980 to 1986 was demonstrated analytically by monitoring of the workers' urine, where it was reported to be present at minimal levels (concentrations were not reported). There was some evidence that the cohort handled other chemicals (including *o*-chloroaniline); however, none of the resulting exposures were quantified by chemical analysis at the time. In other studies, workers were exposed to *p*-chloro-*o*-toluidine and numerous other compounds, several of which are potential carcinogens. No exposure levels were documented, and the exposures occurred before 1980, when modern industrial-hygiene standards were implemented (Ott and Langner 1983, Stasik 1988, IARC 1990, Hogan 1993).

Cancer Studies in Experimental Animals

Dietary administration of *p*-chloro-*o*-toluidine hydrochloride caused benign or malignant blood-vessel tumors (hemangioma or hemangiosarcoma) in the spleen and adipose tissue in mice of both sexes, in two different mouse strains (Weisburger *et al.* 1978, NCI 1979, IARC 1990).

Studies on Mechanisms of Carcinogenesis

p-Chloro-*o*-toluidine caused genetic damage in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (IARC 1990, Goggelmann *et al.* 1996). *p*-Chloro-*o*-toluidine binding to DNA was demonstrated *in vitro* with calf thymus DNA and *in vivo* following administration to mice and rats by intraperitoneal injection (Hill *et al.* 1979, Bentley *et al.* 1986, IARC 2000). In organs from animals exposed to *p*-chloro-*o*-toluidine, DNA breakage was detected by single-cell gel electrophoresis (comet assay) in mouse liver, urinary bladder, lung, and brain and in rat liver and kidney (Sekihashi *et al.* 2002).

Properties

p-Chloro-*o*-toluidine is a chlorinated aromatic amine that exists as a grayish-white crystalline solid or leaflet, and *p*-chloro-*o*-toluidine hydrochloride is a buff-colored or light-pink powder at room temperature. The base compound is practically insoluble in water or carbon tetrachloride but is soluble in ethanol or dilute acid solutions. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of *p*-chloro-*o*-toluidine are listed in the following table. No physical and chemical properties for the hydrochloride were found except its molecular weight of 178.1 and melting range of 265°C to 270°C (IARC 2000, Weisburger 1978).

Property	Information
Molecular weight	141.6[a]
Melting point	30°C[a]
Boiling point	241°C[a]
Log K_{ow}	2.27[b]
Water solubility	0.95 g/L at 25°C[b]
Vapor pressure	0.041 mm Hg at 25°C[b]
Vapor density relative to air	4.9[a]
Dissociation constant (pK_a)	3.85 at 25°C[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

p-Chloro-*o*-toluidine and its hydrochloride salt are used in manufacturing azo dyes for cotton, silk, acetate, and nylon and as intermediates in the production of the dyes C.I. 12800, pigment red 7, and pigment yellow 49 (IARC 1990, 2000). *p*-Chloro-*o*-toluidine has also been used since the 1960s in the manufacture of the pesticide (insecticide and acaricide) chlordimeform. It is believed that chlordimeform is no longer produced or used worldwide (IARC 1990).

Production

Commercial production of *p*-chloro-*o*-toluidine began in Germany in 1924 and was first reported in the United States in 1939 (IARC 1990, 2000). In 2009, *p*-chloro-*o*-toluidine was produced by

two manufacturers in China and one in India (SRI 2009); worldwide, *p*-chloro-*o*-toluidine free base was available from 25 suppliers and the hydrochloride from 5 suppliers (ChemSources 2009). In 1976, U.S. imports of the free base were 25,000 lb (NCI 1979). U.S. imports in a category of substances including *p*-chloro-*o*-toluidine (toluidines and their salts) were 680,000 kg (1.5 million pounds) in 1995, reached a high of 708,000 kg (1.6 million pounds) in 2000, and declined to 209,000 kg (461,000 lb) in 2004. No imports in this category were reported from 1989 to 1994. From 1989 to 2004, U.S. exports in this category ranged from a high of 9.8 million kilograms (22 million pounds) in 1992 to a low of 1.8 million kilograms (3.7 million pounds) in 2002 (USITC 2009). Reports filed in 1986 and 1990 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *p*-chloro-*o*-toluidine totaled 10,000 to 500,000 lb. No inventory update reports for *p*-chloro-*o*-toluidine were filed in 1994 or 1998, and reports in 2002 indicated a quantity of less than 10,000 lb (EPA 2004).

Exposure

The routes of potential human exposure to *p*-chloro-*o*-toluidine are inhalation, ingestion, and dermal contact. The general population can be exposed to *p*-chloro-*o*-toluidine from the use of products that contain it as an impurity; for example, *p*-chloro-*o*-toluidine was found in five samples of finger paints tested in a study in Spain (Garrigos *et al.* 2000). *p*-Chloro-*o*-toluidine hydrochloride has also been found as an impurity in the pesticide chlordimeform (IARC 2000).

p-Chloro-*o*-toluidine could be released to the environment from decomposition of chlordimeform. As of 2000, chlordimeform was not believed to be produced or used anywhere in the world (IARC 2000). Previously, *p*-chloro-*o*-toluidine was isolated and identified in field samples of plant materials treated with chlordimeform. It was measured in young bean leaves at concentrations of less than 0.1 to 0.2 ppm (mg/kg), in grape stems at 0.02 to 0.3 ppm, in a mixture of grape stems and berries at 0.02 to 0.05 ppm, and in prunes and apples at less than 0.04 ppm (Kossmann *et al.* 1971). *p*-Chloro-*o*-toluidine was also reported to be metabolized from chlordimeform by enzymes present in the leaves of apple seedlings and in cotton plants (IARC 1990, 2000). In an experimental field application, residual concentrations of *p*-chloro-*o*-toluidine were found in rice grains at 3 to 61 ppb (µg/kg), in straw parts at 80 to 7,200 ppb, in the upper layer of soil (0 to 5 cm) at 2 to 68 ppb, and in the lower layer of soil (5 to 10 cm) at trace levels to 20 ppb. In another experimental field application of chlordimeform, no residues of *p*-chloro-*o*-toluidine were detected in rice grains or husks tested 20 to 55 days after pesticide application (IARC 1990). Mammals (including dogs, rats, goats, and humans) also metabolize chlordimeform to *p*-chloro-*o*-toluidine.

If *p*-chloro-*o*-toluidine is released to air, it will exist as a vapor and degrade by direct photolysis or photochemically produced hydroxyl radicals, with an estimated half-life of 9 hours. If it is present in water, it will slowly volatilize. It is expected to be moderately mobile in mainly inorganic soils but to bind tightly to soils with high humus or organic-matter content. *p*-Chloro-*o*-toluidine will biodegrade slowly in soil or water and has a low potential for bioaccumulation (HSDB 2009).

p-Chloro-*o*-toluidine has been measured in the urine of workers exposed to chlordimeform; however, no data were found on the levels detected (IARC 1983, 1990). Occupations with the greatest potential for exposure to *p*-chloro-*o*-toluidine include manufacturers of pigments, dyes, and chlordimeform (IARC 2000). Exposures to *p*-chloro-*o*-toluidine were reported to occur during the charging of mixing vats and at the basification stage at a chemical purification facility in England, at a batch-operated chemical processing plant in the United States, and during its production and processing at a facility in Germany. Data on exposure levels were not provided for any of these studies (IARC 1990). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 250 workers (health-services workers and chemists, but not biochemists), all of whom were women, potentially were exposed to *p*-chloro-*o*-toluidine and that 682 workers (health-services and clinical-laboratory workers and health aides, but not nursing aides), including 425 women, potentially were exposed to *p*-chloro-*o*-toluidine hydrochloride (NIOSH 1990b).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for *p*-chloro-*o*-toluidine hydrochloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: *p*-Chloro-*o*-toluidine is a listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *p*-chloro-*o*-toluidine hydrochloride = U049.

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Chromium Hexavalent Compounds

CAS No. 18540-29-9

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Chromium hexavalent (VI) compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies in various geographical locations have consistently reported increased risks of lung cancer among workers engaged in chromate production, chromate pigment production, and chromium plating. Epidemiological studies of lung cancer among ferrochromium workers were inconclusive. Exposure to specific chromium compounds varies by industry. Chromate-production workers are exposed to a variety of chromium compounds, including hexavalent (VI) and trivalent (III) compounds. Chromate-pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds. Epidemiological studies of stainless-steel welders exposed to chromium(VI) compounds also found an increased risk of lung cancer; however, these studies are of limited use for evaluation of chromium's carcinogenicity, because the welders were also exposed to other potential carcinogens. In addition, epidemiological studies of chromate production workers, chromate pigment workers, and chrome platers found an increased risk of a rare cancer of the sinonasal cavity. The data for cancer at sites other than the lung and sinonasal cavity were unclear. The International Agency for Research on Cancer concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate-production, chromate-pigment-production, and chromium-plating industries (IARC 1973, 1979, 1990).

Cancer Studies in Experimental Animals

Exposure to chromium(VI) compounds (calcium chromate, chromium trioxide, or sodium dichromate) via inhalation or intratracheal or intrabronchial implantation caused benign and/or malignant lung tumors in rats and/or mice. Intrabronchial implantation of zinc chromate or strontium chromate also caused bronchial tumors in rats, and inhalation exposure to chromium trioxide caused benign nasal tumors in mice. In addition, cancer at the injection site was observed in rats following administration of chromium compounds (calcium chromate, lead chromate, basic lead chromate, zinc chromate, or strontium chromate) by intrapleural, subcutaneous, or intramuscular injection and in mice following intramuscular injection of calcium chromate (IARC 1980, 1990). IARC (1990) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, lead chromates, strontium chromate, and zinc chromates and limited evidence for the carcinogenicity of chromium trioxide and sodium dichromate.

Since chromium hexavalent compounds were reviewed for listing in the *First Annual Report on Carcinogens* and reviewed by IARC in 1990, the National Toxicology Program has conducted two-year cancer studies of sodium dichromate in rats and mice. Sodium dichromate administered in the drinking water caused cancer of the oral cavity (squamous-cell carcinoma of the oral mucosa) in rats and increased the combined incidence of benign and malignant tumors (adenoma and carcinoma) of the small intestine (duodenum, jejunum, or ileum) in mice (NTP 2008).

Studies on Mechanisms of Carcinogenesis

Chromosomal aberrations, sister chromatid exchange, and aneuploidy were observed in workers exposed to chromium(VI) compounds. Chromium(VI) compounds also caused genetic damage in a variety of test systems. Most caused mutations and DNA damage in bacteria; however, the poorly soluble compounds had to be dissolved in acids or alkalis to produce genetic effects. A few compounds also caused mutations in yeast and insects. Many chromium(VI) compounds caused genetic damage in cultured human and other animal cells and in experimental animals exposed *in vivo*. The compounds tested included ammonium chromate and dichromate, calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, strontium chromate, and the industrial product basic zinc chromate (zinc yellow). Among the types of genetic damage observed were gene mutations (including dominant lethal mutations), DNA damage, sister chromatid exchange, chromosomal aberrations, and cell transformation (IARC 1990).

IARC (1990) concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds based on the combined results of epidemiological studies, cancer studies in experimental animals, and evidence that chromium(VI) ions generated at critical sites in the target cells were responsible for the carcinogenic action observed.

Properties

Elemental chromium is a transition-group metal belonging to group VIB of the periodic table and has oxidation states ranging from −2 to +6, of which the divalent (+2, II), trivalent (+3, III), and hexavalent (+6, VI) forms are the most important. Elemental chromium does not occur naturally in the environment. The divalent (chromous) state is readily oxidized to the more stable trivalent (chromic) state. Although the hexavalent state (including chromates) is more stable than the divalent state, it is rarely found in nature. Chromium(VI) compounds are strong oxidizing agents and are highly corrosive. In the environment, they generally are reduced to chromium(III) compounds. The chromium(VI) compounds most commonly encountered in industry are calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, lead chromate, strontium chromate, and zinc chromate (IARC 1990, Costa 1997). However, this listing applies to all hexavalent chromium compounds, not just to those specified above.

Calcium chromate occurs as yellow crystals or a bright-yellow powder. It is slightly soluble in water and soluble in dilute acids, and it reacts with acids and ethanol. Although calcium chromate is not flammable, toxic chromium fumes may be formed in fires, and mix-

tures with boron burn violently when ignited. Chromium trioxide (also known as chromic trioxide) occurs as dark-red or brown crystals, flakes, or granular powder and is soluble in water, ethyl alcohol, ethyl ether, sulfuric acid, and nitric acid. Contact of chromium trioxide with organic chemicals may result in violent or explosive reactions, and fires with chromium trioxide may produce irritating, corrosive, and toxic gases (ATSDR 2000, HSDB 2009). Lead chromate occurs as yellow, orange, or red crystals or a yellow or orange-yellow powder that is insoluble in water, acetic acid, and ammonia but soluble in dilute nitric acid. When heated, it emits highly toxic fumes, and it may react explosively with azo dyes. The term "lead chromate" is also used to refer to various commercial lead chromate pigments (IARC 1980, 1990, HSDB 2009). Potassium chromate occurs as yellow crystals and is soluble in water but insoluble in ethanol. Potassium dichromate occurs as red or orange-red crystals and is soluble in water but insoluble in ethanol and acetone. It poses a dangerous fire risk when in contact with organic materials or finely divided combustible materials, such as sawdust (ATSDR 2000, HSDB 2009).

Sodium chromate occurs as yellow crystals and is soluble in water and slightly soluble in methanol. Although it is not flammable, toxic chromium oxide fumes may be formed in fires with sodium chromate (ATSDR 2000, HSDB 2009). Sodium dichromate occurs as bright orange-red or red hygroscopic crystals and is soluble in water and methanol. It reacts explosively with hydrazine, acetic anhydride, boron, silicon, and other materials (IARC 1980, HSDB 2009). Strontium chromate occurs as yellow monoclinic crystals or a yellow powder. It is slightly soluble in water and soluble in dilute hydrochloric acid, nitric acid, and acetic acid. It is not flammable but reacts explosively with hydrazine (HSDB 2009). Zinc chromate occurs as lemon-yellow crystals or powder. It is insoluble in cold water and acetone, sparingly soluble in hot water, and soluble in acid and liquid ammonia. Zinc chromate reacts explosively with hydrazine. The term "zinc chromate" is also used to refer to various commercial zinc and zinc potassium chromates (IARC 1990, HSDB 2009). Physical and chemical properties of these chromium(VI) compounds are listed in the following table, along with their chemical formulas.

Use

The steel industry is the major consumer of chromium. In 2007, estimated consumption of chromium in the United States by end use was 78% in stainless and heat-resisting steel, 13.8% for other steel uses, 3.7% in superalloys, and 4.5% in other alloys and end uses (Papp 2009). Alloys of stainless steel and chromium typically contain between 11.5% and 30% chromium (ATSDR 2000). Chromium(VI) compounds are widely used as corrosion inhibitors, in the manufacture of pigments, in metal finishing and chrome plating, in stainless steel production, in leather tanning, and in wood preservatives (Costa 1997, ATSDR 2000). In 1996, about 52% of all chromium compounds used in the U.S. chemical industry were used in production of wood preservatives; the rest were used in leather tanning (13%), metals finishing (13%), pigments (12%), refractories (linings for high-temperature industrial furnaces) (3%), and other uses (7%) (ATSDR 2000). The use of chromium(VI) compounds in wood preservatives increased dramatically from the late 1970s to the early 2000s; however, this use is expected to decrease because of a voluntary phase-out of all residential uses of wood treated with chromated copper arsenate (pressure-treated wood) that went into effect December 31, 2003 (Brooks 2009). Chromium(VI) compounds are also used in textile-dyeing processes, printing inks, drilling muds, pyrotechnics, water treatment, and chemical synthesis (HSDB 2009).

Calcium chromate is used primarily as a corrosion inhibitor and as a depolarizer in batteries (IARC 1973, 1990, HSDB 2009). Chromium trioxide is used primarily in chrome plating and other metal finishing (particularly in the production of automobiles and military aircraft), in production of wood preservatives, as a corrosion inhibitor, and in production of organic chemicals and catalysts. Lead chromate has been used in paints and printing inks and as a colorant in vinyl, rubber, and paper. Potassium chromate is used in production of dyes and in textile-dyeing processes. Potassium dichromate has largely been replaced by sodium dichromate in many applications; however, it is still used in photomechanical processes and production of pigments and wood preservatives. Sodium chromate is used as a corrosion inhibitor and in textile dyeing processes, inks, paints, leather tanning, wood preservatives, drilling muds, cutting oils, water treatment, and production of other chromium compounds. Sodium dichromate is the primary base material for the production of chromium compounds and is used as a corrosion inhibitor, in metal treatments, in drilling muds, and in the production of dyes, wood preservatives, synthetic organic chemicals, and catalysts. Strontium chromate is used as a corrosion inhibitor and metal conditioner, in aluminum flake coatings, as a colorant in polyvinyl chloride, in pyrotechnics, in chrome plating, and for sulfate ion control in electrochemical processes. Zinc chromates are used as corrosion inhibitors and metal conditioners and in paints, varnishes, and oil colors.

Production

The United States is one of the world's leading producers of chromium compounds. U.S. primary production levels of chromium (i.e., mine production of chromite ore) have not been reported since 1961 (USGS 2010). One surface mine was developed in the United States in the mid to late 2000s (Papp 2009, 2010), but production levels have not been reported. Other domestic sources of chromium include recycled stainless-steel scrap, industry stocks, and the Defense National Stockpile. In 2009, the U.S. chromium supply from recycled stainless-steel scrap was 160,000 metric tons (353 million pounds), down from an average of 174,000 metric tons (383 million pounds) from 2000 to 2008 (Papp 2010, USGS 2010). The supply from industry stocks was not reported for 2009; however, this source supplied an average of 10,200 metric tons (23 million pounds) from 2000 to 2008. The government stockpile releases in 2009 were 1,000 metric tons (2.2

Compound	Formula	Molec. wt.	Density (g/cm^3)[a]	Melting pt.	Dec.
Calcium chromate	$CaCrO_4$	156.1	2.89	NR	NR
Chromium trioxide	CrO_3	100.0	2.70	197°C	yes
Lead chromate	$PbCrO_4$	323.2	6.12	844°C	yes
Potassium chromate	K_2CrO_4	194.2	2.73	975°C	NR
Potassium dichromate	$K_2Cr_2O_7$	294.2	2.68	398°C	~500°C
Sodium chromate	Na_2CrO_4	162.0	2.72	792°C	NR
Sodium dichromate	$NaCr_2O_7$	262.0	2.52	357°C	400°C
Strontium chromate	$SrCrO_4$	203.6	3.90	NR	NR
Zinc chromate	$ZnCrO_4$	181.4	3.40	NR	NR

Source: HSDB 2009. [a]Source specifies the temperature at which density was determined for some but not all of the compounds. Dec. = decomposes; NR = not reported.

million pounds), down from an average of 464,000 metric tons (1 billion pounds) from 2000 to 2008. In 2009, U.S. imports of chromium were 150,000 metric tons (331 million pounds), down from an average of 455,000 from 2000 to 2008, and exports were 50,000 metric tons (110 million pounds), down from an average of 181,000 metric tons (400,000 pounds) (Papp 2010). In 2009, apparent consumption of chromium was 260,000 metric tons (573 million pounds), down from average of 538,000 metric tons (1.2 billion pounds) from 2000 to 2008.

U.S. production of calcium chromate in 1977 was at least 5,450 kg (12,000 lb); no other production data and no U.S. import or export data were found. In the late 1970s and early 1980s, annual U.S. production of chromium trioxide was around 30 million kilograms (66 million pounds). Annual production capacity was 52 million kilograms (115 million pounds) in 1988; no more recent data were found. Annual U.S.imports of chromium trioxide ranged from 200,000 kg (440,000 lb) in 1977 to 16.5 million kilograms (36.4 million pounds) in 2002; 2008 imports were 8.9 million kilograms (19.6 million pounds). U.S. exports of chromium trioxide were 4.1 million kilograms (9 million pounds) in 1977, 11.6 million kilograms (25.6 million pounds) in 2000, 8.4 million kilograms (18.5 million pounds) in 2002, and 17.4 million kilograms (38.4 million pounds) in 2008 (IARC 1990, HSDB 2009, USITC 2009).

In 1966, U.S. production of potassium chromate and dichromate combined was estimated at 2.6 million to 3.8 million kilograms (5.7 million to 8.4 million pounds). Production of potassium dichromate declined throughout the 1970s, from 3.2 million kilograms (7.1 million pounds) in 1972 to 1.0 million kilograms (2.2 million pounds) in 1978. No more recent production data for potassium chromate or dichromate were found. In the mid 1980s, combined annual U.S. imports of potassium chromate and dichromate ranged from 580,000 kg (1.3 million pounds) to 1.0 million kilograms (2.2 million pounds) (IARC 1990). U.S. imports of potassium dichromate were 189,000 kg (416,000 lb) in 2002 but only 5,000 kg (11,000 lb) in 2008, while U.S. exports decreased from 26,000 kg (57,000 lb) to 77,000 kg (170,000 lb) (USITC 2009).

The United States produced 139,000 short tons of sodium chromate and dichromate combined in 1998 and 140,700 short tons in 1999 (HSDB 2009). U.S. imports of sodium chromate and dichromate were 4.2 million kilograms (9.3 million pounds) in 1982. Imports of sodium dichromate only were 18.8 million kilograms (41.4 million pounds) in 2002 and 33 million kilograms (72.8 million pounds) in 2008. U.S. exports of sodium chromate and dichromate were 8.8 million kilograms (19.4 million pounds) in 1985 and 26.3 million kilograms (58 million pounds) in 1999. Exports of sodium dichromate only were 12.6 million kilograms (27.8 million pounds) in 2002 and 31.3 million kilograms (69 million pounds) in 2008 (HSDB 2009, USITC 2009).

The United States produced 680,000 kg (1.5 million pounds) of strontium chromate in 1970 (IARC 1990). No other production data were found. U.S. imports of strontium chromate were 300,000 kg (660,000 lb) in 1978, 250,000 kg (550,000 lb) in 1982, 180,000 kg (400,000 lb) in 1984, 390,000 kg (860,000 lb) in 1985, and 120,000 kg (265,000 lb) in 1986 and 1987 (IARC 1990, HSDB 2009). No data on U.S. exports were found. The United States produced 30.6 million kilograms (67 million pounds) of lead chromate in 1972 (HSDB 2009). In 1976 and 1977, 20 million kilograms (44 million pounds) of lead chromate were used annually to produce chrome yellow and chrome orange pigments (IARC 1990). No production data were found for zinc chromate. U.S. imports of lead and zinc chromate combined were 289,000 kg (638,000 lb) in 2000, 135,500 kg (300,000 lb) in 2002, and 8.9 million kilograms (19.6 million pounds) in 2008. U.S. exports were 287,500 kg (634,000 lb) in 2000 and 125,000 kg (275,000 lb) in 2002 (USITC 2009). In 2008, no lead or zinc chromate was imported or exported.

Exposure

Chromium, in the form of unidentified chromium compounds, occurs naturally in the earth's crust and is widely distributed in air, water, soil, and food. Chromium(III) is an essential trace element in humans. The general population is exposed to some chromium(VI) compounds, but the levels of exposure vary. Environmental exposure specifically to chromium(VI) compounds is difficult to quantify, because specific forms of chromium seldom are identified in exposure studies. Although chromium(VI) compounds in the environment may be reduced to chromium(III) compounds, hexavalent forms can persist under some conditions. The general population may be exposed to chromium(VI) compounds through inhalation of ambient air, ingestion of water, or dermal contact with products that contain chromium(VI) compounds, such as pressure-treated wood. People who live near industrial facilities that use chromium(VI) compounds or near chromium waste disposal sites have the greatest potential for exposure (ATSDR 2000).

A 1990 study reported the average concentration of chromium(VI) to be 0.0012 μg/m^3 (range = < 0.001 to 3 μg/m^3) in indoor air samples collected from residences in Hudson County, New Jersey. Other reports of exposure to chromium were not specific for chromium(VI) compounds, but provide general information on exposure to chromium and chromium compounds. Between 1977 and 1984, typical total chromium concentrations in ambient air in the United States were less than 0.01 μg/m^3 in rural areas and 0.01 to 0.03 μg/m^3 in urban areas. Average atmospheric concentrations of chromium from more than 2,100 monitoring stations ranged from 0.005 to 0.525 μg/m^3. A survey of more than 3,800 tap water samples in 1974 and 1975 found chromium concentrations ranging from 0.4 to 8.0 μg/L, with a mean of 1.8 μg/L. In surveys of U.S. surface waters, chromium concentrations in rivers ranged from less than 1 to 30 μg/L, and concentrations in lakes typically were less than 5 μg/L. Typical chromium levels in most fresh foods are low; chromium was detected in vegetables, fruits, grains, cereals, eggs, meat, and fish at concentrations of between 20 and 520 μg/kg. The mean daily dietary intake of chromium was estimated to be less than 0.2 to 0.4 μg from air, 2.0 μg from water, and 60 μg from food (ATSDR 2000).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of chromium compounds since reporting began in 1988 were lowest in 2001 (about half the average from 1988 to 2000). In 2007, 1,384 facilities released 12 million pounds of chromium, and 1,147 facilities released 51 million pounds of chromium compounds. The 100 facilities with the largest releases accounted for most of the total amounts released (TRI 2009).

Most occupational exposure to chromium(VI) compounds is through inhalation or dermal contact. Exposure to specific chromium compounds varies by industry. Chromate production workers are exposed to a variety of chromium compounds, including chromium(VI) and chromium(III) compounds. Chromate pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds.

Occupational exposure to chromium generally exceeds nonoccupational exposure. However, concentrations of airborne chromium in workplaces have declined significantly since the 1980s because of improved emission controls. Typical concentration ranges for airborne chromium(VI) in industries that use chromium(VI) com-

pounds are as follows: stainless-steel welding, 50 to 400 μg/m^3; chromate production, 100 to 500 μg/m^3; chrome plating, 5 to 25 μg/m^3; ferrochrome alloy production, 10 to 140 μg/m^3; and chromate pigment production, 60 to 600 μg/m^3 (IARC 1990, ATSDR 2000). In the tanning industry, hides are soaked with chromium(VI) compounds in the presence of other chemicals that reduce them to chromium(III) compounds (Costa 1997); therefore, exposure in the tanning industry is almost exclusively to soluble chromium(III) (ATSDR 2000). In a study assessing chromium exposure among stainless-steel welders and mild-steel welders, chromium levels in blood, plasma, and urine were higher among the stainless-steel welders, particularly those engaged in manual metal arc welding, which produces fumes with high concentrations of total water-soluble chromium, mainly chromium(VI) (which constituted up to 61% of total soluble chromium) (Edme *et al.* 1997).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 16,576 workers potentially were exposed to chromium (types and compounds not specified), 42,043 to potassium dichromate, and 3,519 to calcium chromate (NIOSH 1976). The National Occupational Exposure Survey (conducted 1981 to 1983) estimated that 386,142 workers, including 10,433 women, potentially were exposed to chromium; 61,073, including 19,198 women, to potassium dichromate; 32,129, including 5,565 women, to calcium chromate; and 30,784, including 8,856 women, to lead chromate (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Chromium compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Chromium compounds are listed as hazardous air pollutants.

Urban Air Toxics Strategy: Chromium compounds have been identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Numerous hexavalent chromium compounds are designated as hazardous substances.

Effluent Guidelines: Chromium and chromium compounds are listed as toxic pollutants.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb for chromium; = 10 lb for chromic acid, sodium chromate, ammonium chromate, potassium chromate, strontium chromate, calcium chromate, lithium chromate, potassium bichromate, ammonium bichromate, sodium bichromate; = 1,000 lb for chromic acetate, chromic sulfate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Chromium compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L for chromium.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chromium hexavalent compounds = F006, F019, K002, K003, K004, K005, K006, K007, K008, K048, K049, K050, K051, K061, K062, K069, K086, K100; on the presence of chromium = F032, F034, F035, F037, F038, K090.

Chromium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.1 mg/L for total chromium.

Food and Drug Administration (FDA)

Maximum permissible level of chromium in bottled water = 0.1 mg/L.

Specified color additives may contain chromium (as chromates) under certain restrictions.

Specified color additives may contain chromium at levels no greater than 50 ppm.

Hydrolyzed leather meal used in the feed of animals may contain chromium at levels not to exceed 2.75% of the total by weight; finished feeds may not contain more than 1% hydrolyzed leather meal by weight.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.005 mg/m^3 for hexavalent chromium and compounds; = 0.1 mg/m^3 where the limit of 0.005 mg/m^3 has been stayed or otherwise is not in effect.

Comprehensive standards have been developed for occupational exposure to hexavalent chromium in any form and in any compound.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.05 mg/m^3 for water-soluble chromium(VI) compounds; = 0.01 mg/m^3 for insoluble chromium(VI) compounds.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 15 mg/m^3 as hexavalent chromium for chromic acid and chromates.

Recommended exposure limit (REL) (time-weighted-average workday) (10-h TWA) = 0.001 mg/m^3 (as hexavalent chromium).

NIOSH considers all hexavalent chromium compounds to be potential occupational carcinogens (based on listings for chromic acid and chromates and for chromyl chloride).

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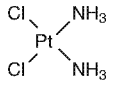
Cisplatin

CAS No. 15663-27-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as *cis*-dichlorodiammineplatinum(II)



Carcinogenicity

Cisplatin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Cisplatin caused tumors in two rodent species and at several different tissue sites. Repeated intraperitoneal injection of cisplatin caused leukemia in rats of both sexes in two studies and increased the incidence of benign lung tumors (adenoma) and number of tumors per animal in female mice. In a similar study in female mice, the incidence of benign skin tumors (papilloma) was increased when croton oil was applied to the skin as a tumor promoter (IARC 1981, 1987a).

Since cisplatin was listed in the *Fifth Annual Report on Carcinogens,* additional studies in rodents have been identified. Cisplatin administered by intraperitoneal injection caused benign lung tumors (adenoma) in female mice (Satoh *et al.* 1993), and a single intraperitoneal injection caused a dose-related increase in liver cancer (hepatocellular carcinoma) in metallothionein-I/II double-knockout mice (which lack a metal-binding protein thought to mitigate the toxicity of various metals) (Waalkes *et al.* 2006). In initiation-promotion studies in mice and rats, cisplatin acted as a tumor initiator following transplacental exposure via a single intraperitoneal injection late in gestation. In mice, transplacental exposure to cisplatin followed by dermal application of 12-*O*-tetradecanoylphorbol-13-acetate at 4 weeks of age initiated the development of benign skin tumors (papilloma). The offspring also developed thymic lymphoma and proliferative kidney lesions (renal-tubular dysplasia) in the presence or absence of the promoter (Diwan *et al.* 1993). In rats, transplacental exposure to cisplatin followed by administration of sodium barbital in the drinking water at 4 weeks of age initiated the development of benign kidney tumors (renal-cell adenoma) in males. Offspring of both sexes developed benign liver tumors (hepatocellular adenoma) in the presence or absence of the promoter (Diwan *et al.* 1995).

Cancer Studies in Humans

No epidemiological studies were available at the time cisplatin was listed in the *Fifth Annual Report on Carcinogens.* Since then, epidemiological studies have been identified, including several large case-control studies of secondary leukemia associated with cisplatin or carboplatin treatment. Excesses of leukemia were found in women treated for ovarian cancer (Kaldor *et al.* 1990, Travis *et al.* 1996) and men treated for testicular cancer (Pederson-Bjergaard *et al.* 1991, Travis *et al.* 1997, Howard *et al.* 2008). However, in most studies, the patients were also exposed to other potentially carcinogenic agents (including carboplatin and doxorubicin hydrochloride) or radiation. No studies to date have attempted to analyze the specific effects of cisplatin on the risk of secondary solid tumors. The studies on solid tumors were also limited by relatively short follow-up times. Cisplatin-based treatment without radiation was associated with a significant increase in the long-term risk of combined secondary solid tumors among five-year survivors of testicular cancer (Van Den Belt-Dusebout *et al.* 2007).

In a number of studies, cisplatin-induced platinum-DNA adducts were observed in tissue culture (IARC 1987b) and in patients receiving cisplatin-based chemotherapy (Reed *et al.* 1993).

Properties

Cisplatin is a metallic (platinum) coordination compound with a square planar geometry that is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and *N,N*-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the *trans*-isomer (IARC 1981, Akron 2009). Physical and chemical properties of cisplatin are listed in the following table.

Property	Information
Molecular weight	300.0
Density	3.74 g/m^3
Melting point	270°C (decomposes)
Log K_{ow}	–2.19
Water solubility	2.53 g/L at 25°C

Source: HSDB 2009.

Use

Cisplatin is a cytostatic agent used for the treatment of various malignancies, often in combination with other antineoplastic agents (IARC 1981, HSDB 2009). Since the 1970s, cisplatin has been used in the treatment of many types of cancer, including soft-tissue and osteogenic sarcoma, Kaposi's sarcoma, retinoblastoma, neuroblastoma, Wilm's tumor, gestational trophoblastic tumors, and cancer of the ovary, uterus, endometrium, cervix, prostate, urinary bladder, anaus, vulva, testis, adrenal gland, lymphatic system, head and neck, skin, esophagus, thyroid gland, lung (other than small-cell cancer), breast, liver (including hepatoblastoma), stomach, and bile duct (IARC 1981, MedlinePlus 2003).

Production

Preparation of cisplatin was reported in the 1840s (IARC 1981). In 2009, cisplatin was produced by eleven manufacturers worldwide, including four in India, three in Central and South America, two in Europe, one each in China and Mexico, and none in the United States (SRI 2009). It was available from 35 suppliers, including 23 U.S. suppliers (ChemSources 2009), and seven drug products with cisplatin as the active ingredient were produced by five pharmaceutical companies (FDA 2009).

Exposure

Cisplatin is used in human medicine to treat a variety of malignancies (IARC 1981). It is available as injectable solutions at a concentration of 1 mg/mL, in 10- or 50-mg vials. The usual intravenous dose of cisplatin is 20 mg/m^2 of body surface per day for five days or 100 mg/m^2 once every four weeks. Doses as high as 40 mg/m^2 daily for five consecutive days have been used (Chabner *et al.* 2001). Manufacturing and health-care workers, including housekeeping personnel, potentially are exposed to cisplatin during its production, preparation, or administration or during cleanup of medical waste, including excretions of patients treated with cisplatin. Occupational exposure to chemotherapeutic drugs was demonstrated in a study which found that urine of nurses who administer these agents was mutagenic in bacteria-based assays (Falck *et al.* 1979). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 21,216

U.S. health-services workers, including 15,289 women, potentially were exposed to cisplatin (NIOSH 1990).

Environmental release of cisplatin may occur during its manufacture and through disposal of medical wastes (Zimmerman *et al.* 1981, NIOSH 2004, HSDB 2009). If released to water, cisplatin is likely to remain in solution and transform slowly to the trans form. If released to soil, it is likely to leach into the subsurface. Cisplatin has been shown to be nonbiodegradable (HSDB 2009).

Regulations

Food and Drug Administration (FDA)

Cisplatin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Coal Tars and Coal-Tar Pitches

CAS No. 8007-45-2 (Coal Tar)

No separate CAS No. is assigned to coal-tar pitches

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Coal tars and coal-tar pitches are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous studies, mostly case reports, have found that occupational exposure to coal tars or coal-tar pitches (coal-tar distillates) is associated with skin cancer, including scrotal cancer; workers in these studies have included patent-fuel (coal-briquette) workers, pitch loaders, workers in electrical trades, and optical-lens polishers (IARC 1985, 1987). A 1946 study in the United Kingdom found that patent-fuel workers were 500 times as likely as other workers to die of scrotal cancer. In addition, there have been many case reports of skin cancer among patients using therapeutic coal-tar preparations. Occupational exposure to coal tars or coal-tar pitches has also been associated with cancer at other tissue sites, including the lung, bladder, kidney, and digestive tract. Excesses of lung cancer were found in several epidemiological studies of workers exposed to coal-tar fumes in coal gasification and coke production, in studies of workers exposed to pitch fumes in aluminum production and calcium carbide production, and in a study of millwrights and welders exposed to coal-tar pitches and coal tars. The millwrights and welders also showed increased risks of digestive-tract cancer and leukemia. The risk of bladder cancer was increased in tar distillers and patent-fuel workers exposed to coal tars and coal-tar pitches and in aluminum production workers exposed to coal-tar pitches. The risk of kidney (renal-pelvis) cancer was increased in workers exposed to "petroleum or tar or pitch." Studies of roofers, who are exposed to coal-tar pitches, have found increased risks of cancer at other tissue sites in addition to skin, bladder, and lung cancer and leukemia, including cancer of the oral cavity, larynx, esophagus, and stomach; however, roofers are also exposed to other potentially carcinogenic agents, such as asphalt.

Cancer Studies in Experimental Animals

Dermal exposure to coal tars (including pharmaceutical and high-temperature coal tars) or coal-tar extracts caused skin tumors in mice and rabbits and lung cancer (but not skin tumors) in rats. Inhalation

exposure to coal tar from coke ovens caused skin tumors in mice and lung tumors in mice and rats. An extract of a coal-tar fume condensate administered by intramuscular injection caused tumors at the injection site (sarcoma) in mice. Dermal exposure to coal-tar pitches or coal-tar pitch extracts caused benign and malignant skin tumors in mice (IARC 1985, 1987).

Studies on Mechanisms of Carcinogenesis

Both coal tars and coal-tar pitches contain a number of known and potential carcinogens, including benzene, naphthalene, and other polycyclic aromatic hydrocarbons (PAHs). Coal-tar pitch extracts showed both tumor-initiating and tumor-promoting activity in mouse skin (IARC 1985, 1987).

Properties

Coal tars are by-products of the destructive distillation (carbonization) of coal to produce coke or gas. The composition and properties of a coal tar depend primarily on the temperature of the carbonization and to a lesser extent on the nature (source) of the coal used as feedstock. In general, coal tars are complex combinations of hydrocarbons, phenols, and heterocyclic oxygen, sulfur, and nitrogen compounds. Over 400 compounds have been identified in coal tars, and as many as 10,000 may actually be present. The PAH content of coal tars increases with increasing carbonization temperature. Coal tars typically are black or almost-black viscous liquids or semisolids with a characteristic naphthalene-like odor (ATSDR 2002). They are slightly soluble in water, partially soluble in acetone, carbon disulfide, chloroform, diethyl ether, ethanol, methanol, petroleum ether, and sodium hydroxide, and soluble in benzene and nitrobenzene. Low-temperature coal tars (formed at temperatures below 700°C) are black, viscous liquids that are denser than water and contain a lower percentage (40% to 50%) of aromatic compounds than high-temperature coal tars (IARC 1985). Coal tars are highly flammable and corrosive, and toxic gases may be released when they burn. Their vapors can form explosive mixtures with air (HSDB 2009).

Coal-tar pitches are shiny, dark-brown to black residues produced during the distillation of coal tars. They contain various PAHs, their methyl and polymethyl derivatives, and heteronuclear compounds (IARC 1985).

Use

Coal tars and coal-tar pitches have many uses in industry and in consumer products. Coal tars are used primarily for the production of refined chemicals and coal-tar products, such as creosote, coal-tar pitch, and crude naphthalene and anthracene oils from the distillation of crude coal tar. Coal tar has been used as a fuel in open-hearth furnaces and blast furnaces in the steel industry, as a binder and filler in surface-coating formulations, and as a modifier for epoxy-resin surface coatings. U.S. Pharmacopeia–grade coal tar is approved for use in denatured alcohol (IARC 1985). Coal-tar preparations have been used for many years to treat various skin conditions, such as eczema, psoriasis, seborrheic dermatitis, and dandruff. Both prescription and nonprescription preparations are available and include cleansing bars, creams, gels, lotions, ointments, shampoos, and other topical solutions and suspensions (DermNet NZ 2010). Coal tar is also registered as an active ingredient in pesticides with the U.S. Environmental Protection Agency (EPA 2003).

Coal-tar pitches are used primarily as the binder for aluminum-smelting electrodes (IARC 1984). They are also used in roofing materials, to impregnate and strengthen refractory brick (for lining industrial furnaces), and in surface coatings, such as pipe-coating enamels and black varnishes used as protective coatings for industrial steelwork and as antifouling paints for boats. Hard pitch is used as a binder for foundry cores. Coke-oven pitch is used to produce pitch coke, which is used as the carbon component of electrodes, carbon brushes, and carbon and graphite articles. Distillation fractions and residues from high-temperature coal tars are used for road paving and construction and in the production of naphthalene, recovery of benzene, production of anthracene paste, briquetting of smokeless solid fuel, impregnation of electrodes and fibers, and manufacture of electrodes and graphite (IARC 1985).

Production

Coal tar was first produced in the United States in 1913, when over 1.0 billion pounds was produced as a by-product of coke production (IARC 1985). Because the majority of coal tar is produced by the steel industry, its production depends on the demand for steel. U.S. coal-tar production was 168.6 million gallons in 1986, 188.5 million gallons in 1987 (ATSDR 2002), and 1.8 billion pounds in 1994 (USITC 1995). In 2009, six U.S. suppliers of coal tar and one U.S. supplier of coal-tar pitch were identified (ChemSources 2009).

Exposure

The primary routes of potential human exposure to coal tars and coal-tar products are inhalation, ingestion, and dermal contact. The general population may be exposed to coal tar through its use in treating skin disorders. It has been estimated that nearly 2% of the United States population is affected by psoriasis, one of the conditions for which coal-tar ointments (containing 1% to 10% coal tar) are prescribed (IARC 1985). Others may be exposed through the use of coal-tar shampoos to treat dandruff or coal-tar ointments to treat eczema. The general population may also be exposed to coal tars present as environmental contaminants (ATSDR 2002).

Occupational exposure to coal tars and coal-tar pitches may occur at foundries and during coke production, coal gasification, and aluminum production. Coal gasification and iron and steel foundry workers potentially are also exposed to coal-tar pitch volatiles, including a variety of PAHs (IARC 1984). Coke ovens are the primary source of coal tar (NIOSH 1977). In 1970, the United States had 64 coking plants operating more than 13,000 coke ovens, with about 10,000 workers (NIOSH 1973). The numbers of plants and ovens remained essentially the same through 1975 but by 1998 had declined to 23 coking plants operating about 3,800 ovens (EPA 2001). In the early 1970s, an estimated 145,000 workers were directly or indirectly involved with coal-tar products (NIOSH 1977). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 1,354 workers potentially were exposed to coal-tar pitch (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 7,274 workers (including 42 women) potentially were exposed to coal tar, 19,021 workers (including 98 women) to coal-tar pitch, and 7,677 workers (including 78 women) to coal-tar-pitch volatiles (NIOSH 1990). No more recent occupational exposure surveys were found.

Workers potentially exposed to coal-tar pitches include those producing or using pavement tar, roofing tar, coal-tar pitch, coal-tar paints, coal-tar enamels, other coal-tar coatings, or refractory bricks. The concentrations of PAHs in ambient air ranged from 0 to 200 $\mu g/m^3$ near roof-tarring operations and from 0 to 3,700 $\mu g/m^3$ near pavement-tarring operations. Another study found that coal-tar pitch workers at a U.S. roofing site inhaled up to 53 µg of benzo[*a*]pyrene in seven hours (Hammond *et al.* 1976). The potential for skin exposure may be considerable; because of the heat, workers often wear little clothing, thereby exposing large portions of the body to coal tars or coal-tar pitches. In the skin oil of nine roofing workers (potentially

exposed to coal-tar pitch and bitumen), 0.000048 to 0.036 µg of PAHs were detected in a 36-cm^2 area of the forehead (Wolff *et al.* 1982).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of coal-tar pitches on ships and barges.

Department of Transportation (DOT)

Flammable coal-tar distillates are considered a hazardous material, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Air emissions of hazardous air pollutants from the handling of coal tar are regulated under certain source categories.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of certain coal-tar residues = K141, K142, K147, K148.

Coal-tar creosote is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Any drug products containing coal tar at levels of 0.5% to 5% must contain a label specifying the identity and concentration of the coal tar.

Any hair dye containing coal tar must display a warning label stating that the product contains an ingredient that has been determined to cause cancer in laboratory animals.

Certain dermal products containing coal tar must provide warning labels of specific precautions for that product.

The use of coal tar in several over-the-counter drugs is no long recognized as safe and effective for the specified uses.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit = 0.2 mg/m^3 for coal-tar-pitch volatiles – benzene-soluble fraction.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m^3 for coal-tar-pitch volatiles as benzene-soluble aerosol.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.1 mg/m^3 for coal-tar-pitch volatiles and coal-tar products – cyclohexane-extractable fraction.

Immediately dangerous to life and health (IDLH) limit = 80 mg/m^3 for coal-tar-pitch volatiles.

Coal-tar-pitch volatiles are listed as potential occupational carcinogens.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

References

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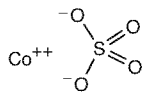
Cobalt Sulfate

CAS No. 10124-43-3

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Cobalt sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to cobalt sulfate by inhalation caused tumors in two rodent species and at two different tissue sites. For inhalation-exposure studies in rodents, the exposure atmospheres were generated as aerosols of cobalt sulfate heptahydrate, containing cobalt ions, sulfate ions, and water, which were partially dried before they entered the exposure chambers. (The hydrated and non-hydrated forms of a solute behave similarly when dissolved in water, both forming a solution of hydrated ions and water.) Inhalation exposure to cobalt sulfate heptahydrate caused lung cancer (alveolar/bronchiolar carcinoma) in mice of both sexes and in female rats, and it increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in male rats. It also increased the combined incidence of benign and malignant adrenal-gland tumors (pheochromocytoma) in female rats (NTP 1998).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the carcinogenicity of exposure specifically to cobalt sulfate. However, several studies evaluated the carcinogenicity of cobalt compounds as a class. Most of these studies investigated the effects of occupational exposure to hard metals (cobalt and tungsten carbide) or metallic cobalt (Lasfargues *et al.* 1994, Moulin *et al.* 1998, Wild *et al.* 2000). Although these studies consistently reported an increased risk of lung cancer among workers exposed to cobalt, the workers were also exposed to other agents (e.g., tungsten carbide) and probably were not exposed to soluble cobalt. Thus, these studies are of uncertain rele-

vance for evaluating whether exposure specifically to cobalt sulfate causes cancer. Only one study investigated the effects of exposure to cobalt salts. The initial study reported an increased risk of lung cancer among cobalt production workers, but a follow-up study of the same workers found no increased risk of cancer (Mur *et al.* 1987, Moulin *et al.* 1993). Interpretation of this finding is limited by the small number of exposed workers who developed cancer.

Studies on Mechanisms of Carcinogenesis

Cobalt sulfate did not cause mutations in most bacterial test systems studied, but it did cause genetic damage in many test systems using mammalian cells (NTP 1998). In Syrian hamster embryo cells, cobalt sulfate caused cell transformation (Kerckaert *et al.* 1996) and micronucleus formation (Gibson *et al.* 1997). In mouse fibroblasts, it caused expression of the *p53* tumor-suppressor gene (Duerksen-Hughes *et al.* 1999). In the presence of hydrogen peroxide, cobalt sulfate induced single-strand breaks and apparent intrastrand cross-links in DNA, but not the formation of 8-hydroxy-2′-deoxyguanosine adducts (Lloyd *et al.* 1997, 1998). In human lymphocytes, cobalt sulfate heptahydrate decreased the mitotic index but did not cause micronucleus formation or chromosomal aberrations (Olivero *et al.* 1995).

As a constitutent of vitamin B_{12} (cobalamin), cobalt is absorbed from the gastrointestinal tract, lungs, and skin and is distributed throughout the body. The highest concentrations are found in the liver, kidney, and heart. Cobalt is eliminated primarily in the urine, in two phases: the first phase is rapid and occurs within days, and the second may take several years (Léonard and Lauwerys 1990). The mechanism by which cobalt ions cause cancer has not been determined. It has been suggested that cobalt may replace other essential divalent metal ions (e.g., magnesium, calcium, iron, copper, or zinc), thus altering important cellular functions. Other potential mechanisms include inhibition of DNA repair and interaction with hydrogen peroxide to form reactive oxygen species that can damage DNA (Beyersmann and Hartwig 1992, Lison *et al.* 2001).

Properties

Cobalt sulfate is a cobalt compound that is a reddish to lavender crystalline solid at room temperature. It is soluble in water, sparingly soluble in methanol, and insoluble in ammonia. It is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of cobalt sulfate are listed in the following table.

Property	Information
Molecular weight	155.0
Specific gravity	3.71 at 25°C/4°C
Melting point	735°C
Water solubility	383 g/L at 25°C

Source: HSDB 2009.

Use

Cobalt sulfate is used in the electroplating and electrochemical industries; as a drier for lithographic inks, varnishes, paints, and linoleum; in storage batteries; and as a coloring agent in ceramics, enamels, glazes, and porcelain. In addition, cobalt sulfate has been used in animal feeds as a mineral supplement (Budavari *et al.* 1996, Richardson 2003) and on pastures where the forage is cobalt deficient, to provide enough cobalt for ruminants (e.g., cattle, sheep, or goats) to produce vitamin B_{12} (EPA 1999, Washington State 1999). Past uses include addition to beer to improve the stability of the foam (NTP 1998), prevention and treatment of cobalt deficiency in ruminants, and administration to improve blood values (hematocrit, hemoglobin, and erythrocyte levels) in people with forms of anemia not responsive to other treatments (Hillman and Finch 1985, HSDB 2009).

Production

Cobalt sulfate is formed by the interaction of cobalt oxide, hydroxide, or carbonate with sulfuric acid. Production of cobalt sulfate in the United States in 1983 was estimated at 450,000 lb (NTP 1998). No more recent production data were available. Cobalt is no longer mined or refined in the United States, but negligible amounts are produced as by-products of other mining operations (USGS 2003). In 2009, cobalt sulfate was available from 18 U.S. suppliers (ChemSources 2009). In 1986, U.S. imports of cobalt sulfate were 79,700 lb (HSDB 2009). Between 1995 and 2001, annual imports ranged from about 900 metric tons to over 1,600 metric tons (2 million to 3.5 million pounds) (Shedd 2003). No information was found on U.S. exports of cobalt sulfate.

Exposure

No information was found on environmental exposure specifically to cobalt sulfate. The general population may be exposed to cobalt through inhalation of ambient air or ingestion of food or drinking water. Cobalt is an essential trace element in humans, because a cobalt atom is present in each molecule of vitamin B_{12} (Anderson 2000). The 1999 National Health and Nutrition Examination Survey reported the geometric mean cobalt level in the urine of humans to be 0.36 µg/L of urine (95% confidence interval = 0.32 to 0.40) (CDC 2001).

No information was found on occupational exposure specifically to cobalt sulfate. However, more than a million U.S. workers potentially are exposed to cobalt or cobalt compounds (Jensen and Tüchsen 1990). Occupational exposure to cobalt occurs mainly in refining processes, in production of alloys, and in the tungsten carbide hardmetal industry (Kazantzis 1981). In addition, many workers receive limited exposure when using cobalt-containing paint driers. Occupational exposure is primarily dermal or through inhalation of cobalt metal dusts or fumes (NTP 1998, HSDB 2009). Among workers exposed to cobalt, the concentrations of cobalt in blood and urine are closely related to the average levels of cobalt in the air during a workweek (Alexandersson 1988).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Cobalt compounds are listed as hazardous air pollutants.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt compounds are listed and subject to reporting requirements.

Food and Drug Administration (FDA)

Cobaltous salts are prohibited from use in human food.

All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives) have been withdrawn from the market because they were found to be unsafe or not effective, and they may not be compounded.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m^3 for cobalt and inorganic cobalt compounds.

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Cobalt–Tungsten Carbide: Powders and Hard Metals

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Co/WC, WC/Co

Carcinogenicity

Cobalt–tungsten carbide powders and hard metals are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Epidemiological studies provide evidence for the carcinogenicity of cobalt–tungsten carbide powders and hard metals based on (1) consistent findings of excess lung-cancer mortality among cobalt–tungsten carbide hard-metal manufacturing workers across studies, (2) higher risks among individuals with higher exposure levels, and (3) positive exposure-response relationships that cannot be explained by confounding with tobacco smoking. However, the epidemiological data are limited, because there are few studies of independent populations.

The published epidemiological literature consists of mortality studies of two independent multi-plant cohorts of cobalt–tungsten carbide hard-metal manufacturing workers, one in France (Moulin *et al.* 1998) and one in Sweden (Hogstedt and Alexandersson 1990), and cohort studies of two individual factories included in the French multi-plant cohort (Lasfargues *et al.* 1994, Wild *et al.* 2000). The French multi-plant cohort included all 10 cobalt–tungsten carbide manufacturing plants in France; in addition, a nested case-control study of lung cancer was conducted within this cohort. The nested case-control study is most informative for evaluating cancer risk, because it used a semi-quantitative exposure scale to evaluate exposure-response relationships and considered potential confounding by exposure to tobacco smoking and other known or suspected occupational carcinogens. The cohort study of the largest French factory shares these advantages; however, because the workers were included in the multi-plant study, it does not provide independent evidence for carcinogenicity. In these two studies, four metrics of exposure were evaluated: (1) exposure level, which was the highest exposure score experienced during an individual's work history (on a scale of 0 to 9), (2) duration of exposure at a level of 2 or higher, (3) unweighted cumulative dose, which assigned the same level to occasional and full-time exposure, thus favoring peak exposure, and (4) frequency-weighted cumulative dose, which weighted exposure level by the frequency of exposure, thus reducing the effect of occasional exposure. The Swedish study, although limited in size, provides supporting information for an independent population.

Excess lung-cancer mortality (of approximately 30%) was found in both multi-plant cohort studies (Hogstedt and Alexandersson 1990, Moulin *et al.* 1998); risk estimates were significantly higher among individuals with higher measures of exposure or longer time since first exposure (latency). In the nested case-control study (Moulin *et al.* 1998), lung cancer risk was significantly higher (odds ratio [OR] = 1.93, 95% CI = 1.03 to 3.62, 35 exposed cases) among workers exposed to cobalt–tungsten carbide (exposure level ≥ 2) than among workers with little or no exposure (exposure level < 2). In exposure-response analyses using workers in the lowest exposure category as the comparison group, lung-cancer risk was significantly higher (by up to fourfold) for workers in the highest categories of both measures of cumulative dose, and an elevated risk of borderline statistical significance was found for workers in the highest exposure-level category. Positive exposure-response relationships were observed for all four measures of exposure: duration (P_{trend} = 0.03), unweighted cumulative dose (P_{trend} = 0.01), frequency-weighted cumulative dose (P_{trend} = 0.08), and exposure level (P_{trend} = 0.08). Adjustment for tobacco smoking or exposure to known or suspected carcinogens did not change the results. The Swedish study had limited ability to evaluate exposure-response relationships because of small numbers of exposed workers with lung cancer. Nevertheless, the risk of lung cancer mortality was significantly increased for workers with exposure duration

of over 10 years and latency of over 20 years (standardized mortality ratio [SMR] = 2.78, 95% CI = 1.11 to 5.72, 7 exposed cases). Analyses restricted to workers with at least 10 years' exposure or at least 20 years' latency found somewhat higher SMRs for "high-exposed" than "low-exposed" workers (Hogstedt and Alexandersson 1990).

Excess risks of lung-cancer mortality were also found in studies of the two individual French factories. Wild *et al.* (2000) reported significantly elevated SMRs (by approximately twofold) for lung cancer among all male workers and among male workers ever employed in presintering workshops or with exposure levels of at least 2. The highest SMRs were observed for male workers in the highest exposure categories of all four exposure metrics (level, duration, and both measures of cumulative dose), although the trends were not statistically significant, and the risk estimates were imprecise. In the study by Lasfargues *et al.* (1994), the entire cohort had a significantly increased risk of lung cancer, and the risk was highest among workers in the highest exposure-level category. Although small, this study provides supporting evidence that the findings for the French industry-wide cohort were not due solely to the results for the large factory studied by Wild *et al.*

Both the French multi-plant cohort study (Moulin *et al.* 1988) and the larger study of an individual French factory (Wild *et al.* 2000) found higher risks of lung cancer for exposure to cobalt–tungsten carbide before sintering than after sintering (see Production). The authors stated that exposure was highest during presintering processes; however, there is no evidence of toxicological differences between presintered and sintered materials, and both materials release similar amounts of cobalt ions (see Studies on Mechanisms of Carcinogenesis).

It is unlikely that the excess risks of lung cancer found in the French studies were due to confounding by tobacco smoking or coexposure to other known carcinogens. In the multi-plant study, the smoking-adjusted odds ratio for cobalt–tungsten carbide exposure (OR = 2.6, 95% CI = 1.16 to 5.82) was similar to the unadjusted risk (OR = 2.29, 95% CI = 1.08 to 4.88). Neither study found increased risks of smoking-related diseases, such as chronic bronchitis and emphysema, and adjustment for smoking or exposure to other occupational carcinogens did not change the findings in the exposure-response analyses (Moulin *et al.* 1988, Wild *et al.* 2000). Neither the Swedish multi-plant study (Hogstedt and Alexandersson 1990) nor the small French cohort study (Lasfargues *et al.* 1994) adjusted for smoking; however, surveys of smoking habits among a subset of workers found smoking rates similar to those in the general population. Overall, the studies are limited by the lack of quantitative exposure assessment and potential confounding; however, exposure misclassification would most likely reduce the likelihood of detecting a true effect.

Studies on Mechanisms of Carcinogenesis

The findings from epidemiological studies are supported by studies on mechanisms of carcinogenesis. Although the mechanism(s) by which by cobalt–tungsten carbide causes cancer have not been fully elucidated, it has been shown that (1) cobalt–tungsten carbide releases cobalt ions, (2) cobalt ions affect biochemical pathways related to carcinogenicity, (3) cobalt compounds are carcinogenic in experimental animals, (4) cobalt–tungsten carbide increases the production of reactive oxygen species (ROS) and causes greater cytotoxic, toxic, and genotoxic effects than does cobalt alone, (5) cobalt–tungsten carbide causes key events related to carcinogenesis, including genotoxicity, cytotoxicity, inflammation, and apoptosis (programmed cell death), and (6) the oxidative stress response resulting from increased ROS production may play a role in these key events and may also interfere with cells' ability to repair damage caused by cobalt–tungsten carbide. The combination of the effects from cobalt ions and the oxidative stress response from ROS production provide plausible modes of action for the carcinogenicity of cobalt–tungsten carbide.

Studies in biological fluids, *in vitro* systems, experimental animals, and humans have demonstrated that cobalt is rapidly solubilized from cobalt–tungsten carbide. Cobalt dissolution rates were similar for presintered and sintered cobalt–tungsten carbide incubated in various artificial biological fluids (Stopford *et al.* 2003). Tungsten is not rapidly solubilized from cobalt–tungsten carbide, but can be phagocytized by macrophages (Lombaert *et al.* 2004). Cobalt was also released from hard-metal dust incubated with plasma and lung tissue (Edel *et al.* 1990). In experimental animals administered cobalt–tungsten carbide by intratracheal administration, cobalt was solubilized rapidly, cleared from the lung, distributed in the body, and excreted in the urine (Lison 1996). Rats exposed intratracheally to cobalt–tungsten carbide had more cobalt in the urine than did rats administered cobalt alone, suggesting that tungsten carbide increases the bioavailability of cobalt (Lasfargues *et al.* 1992). Several biomonitoring studies detected elevated levels of cobalt in the urine, lungs, and other tissues of workers exposed to cobalt–tungsten carbide hard metals (Rizzato *et al.* 1986, Nicolaou *et al.* 1987, Gallorini *et al.* 1994, Sabbioni *et al.* 1994b, Scansetti *et al.* 1994, 1998, Linnainmaa and Kiilunen 1997, Goldoni *et al.* 2004).

Soluble cobalt compounds are genotoxic and carcinogenic in experimental animals. Cobalt sulfate is listed as *reasonably anticipated to be a human carcinogen* in the Report on Carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals. Specifically, inhalation exposure to cobalt sulfate in rodents caused lung tumors (adenoma or carcinoma) in mice and rats and adrenal-gland tumors (pheochromocytoma) in female rats (Bucher *et al.* 1999). Cobalt ions produce ROS, which cause oxidative DNA damage and act on a number of cancer-related molecular targets. Cobalt ions disrupt cell-signaling pathways (Murata *et al.* 1999), inhibit DNA repair (Hartwig 2000, Hartwig *et al.* 2002), regulate genes involved in the response to hypoxia (Beyersmann 2002), replace or mimic essential divalent metal ions, thus altering cellular reactions (Nackerdien *et al.* 1991, Beyersmann and Hartwig 1992, Kawanishi *et al.* 1994, Lloyd *et al.* 1998), and interfere with mechanisms involved in cell-cycle control and modulation of apoptosis (DeBoeck *et al.* 2003b,c).

Numerous *in vitro* studies (reviewed in NTP 2009) and *in vivo* studies (Huaux *et al.* 1995, Lasfargues *et al.* 1995) have shown greater cytotoxic effects (measured primarily by lactate dehydrogenase release) for cobalt–tungsten carbide than for either cobalt powder or tungsten carbide alone. The mixture's greater *in vitro* toxicity to macrophages is not fully explained by greater bioavailability of cobalt (Lison and Lauwerys 1992, 1994). Respirable samples collected at various stages of the hard-metal manufacturing process (including powders for pressing, presintered materials, and powders from grinding of sintered materials) caused cytotoxicity and pathological changes in the lungs of rats after intratracheal injection (Adamis *et al.* 1997). In addition, cobalt–tungsten carbide causes a type of respiratory toxicity ("hard-metal disease") that is not observed with exposure to cobalt alone. Hard-metal disease is characterized by a giant-cell interstitial pneumonia that can develop into lung fibrosis (Lison 1996, Lison *et al.* 1996).

There is some evidence that the greater toxicity of cobalt–tungsten carbide may result from a physicochemical reaction that takes place at the interface between certain carbides and cobalt particles (Lison and Lauwerys 1992). The structural features of the two particles may help to explain the effects. Cobalt metal can reduce ambient oxygen, but only at a low rate of reaction, because of the particles' surface characteristics. Tungsten carbide is inert and does not react with oxygen

but is a good electron conductor. When cobalt and tungsten carbide particles are associated, the cobalt electrons are transferred to the carbide surface, allowing increased oxygen reduction and thus increased production of ROS. Biochemical studies on the production of ROS have shown that cobalt's capacity to generate hydroxyl radicals is greatly increased by association with tungsten carbide. Formation of the ROS results directly from the interaction of cobalt with tungsten carbide or indirectly from the cobalt ions generated from the Fenton-like reaction of the cobalt metal with the carbide (Lison and Lauwerys 1993, Lison *et al.* 1995). In oxygen-radical-generating systems, post-sintered powders sampled from final machining (grinding) of cobalt–tungsten carbide products produced higher levels of ROS than did pre-sintered samples of cobalt and tungsten carbide separately or as mixtures (Stefaniak *et al.* 2010).

Metal-induced generation of ROS in cellular test systems leads to oxidative stress as a result of increased free radicals and insufficient antioxidative defense. Protective mechanisms include cellular antioxidant systems, the stress-protein response, and the involvement of DNA excision and repair enzymes (Kasten *et al.* 1997, Shi *et al.* 2004, Lombaert *et al.* 2008). Fenoglio *et al.* (2008) studied oxidation of the antioxidant glutathione and cysteine sulfhydryl groups by cobalt–tungsten carbide dust–induced ROS and reported dust-concentration-dependent generation of thiyl radicals at particle surface sites. Depletion of cellular antioxidant defenses could further exacerbate cellular oxidative damage caused by ROS generated by cobalt–tungsten carbide particles.

Regulation of gene expression, including apoptotic, stress-protein, and immune-response pathways, also can be affected by ROS. Lombaert *et al.* (2008) evaluated the effects of cobalt–tungsten carbide exposure *in vitro* on patterns of gene expression in human peripheral-blood mononucleated cells and reported statistically significant up-regulation of apoptosis and stress or defense response pathways and down-regulation of immune-response pathways.

Apoptosis has been associated with exposure to a number of known carcinogens (arsenic, cadmium, chromium, nickel, and beryllium) and possible carcinogens (cobalt and lead). Cobalt chloride has been shown to induce apoptosis through formation of ROS in both human alveolar macrophages and a rat pheochromocytoma cell line (PC12); co-administration of antioxidants suppressed ROS production and restored cell viability (Zou *et al.* 2001, Araya *et al.* 2002). Cobalt–tungsten carbide, tungsten carbide, and cobalt ions induced apoptosis in human lymphocytes; the effect of the mixture was significantly greater than that of tungsten carbide or cobalt alone (Lombaert *et al.* 2004).

Cobalt–tungsten carbide is genotoxic *in vitro* and causes mutations in the lungs of rats exposed *in vivo*. Its genotoxicity (clastogenic effects) may be caused by increased ROS production from the interaction between cobalt and tungsten carbide, from ionic cobalt, or from both. In addition, cobalt ions inhibit DNA repair, which may also contribute to cobalt–tungsten carbide's genotoxic effects. Specifically, cobalt–tungsten carbide caused DNA strand breaks in mouse 3T3 fibroblasts and human peripheral-blood lymphocytes (Anard *et al.* 1997) and micronucleus formation in human peripheral-blood lymphocytes (Van Goethem *et al.* 1997, De Boeck *et al.* 2003c). In these studies, cobalt–tungsten carbide was more genotoxic than cobalt alone. In rats exposed by intratracheal instillation, cobalt–tungsten carbide caused DNA damage and micronucleus formation in the lung (type II pneumocytes) (De Boeck *et al.* 2003a). No increase in DNA damage or micronucleus formation was observed in rat peripheral-blood lymphocytes; however, it is unclear whether circulating lymphocytes are a good reporter for monitoring genotoxic effects from inhaled particles. In humans, neither DNA damage nor micronucleus formation was increased in lymphocytes of cobalt–tungsten carbide hard-metal workers, compared with unexposed workers; however, this study was limited by small sample size (De Boeck *et al.* 2000). Multiple regression analyses (Mateuca *et al.* 2005) indicated that both end points were associated with an interaction between tobacco smoking and exposure, and that micronucleus formation was associated with smoking, working in a cobalt–tungsten carbide plant, and having variant forms of genes coding for DNA repair enzymes (X-ray repair cross-complementing group 3 and 8-oxoguanine DNA glycosylase).

In addition, although the pathogenesis of hard-metal disease is not fully understood, it may involve differences in the susceptibility (genetic and/or health-related) of affected individuals to the toxic effects of increased ROS production due to cobalt–tungsten carbide exposure. Further, the mechanisms for fibrosing alveolitis and lung cancer in hard-metal workers may be related, conceivably involving oxidative damage and/or inflammatory events (IARC 2006).

Cancer Studies in Experimental Animals

No studies in experimental animals were identified that evaluated the relationship between cancer and exposure specifically to cobalt–tungsten carbide powders or hard metals.

Properties

This listing includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide. Powders containing both cobalt and tungsten carbide may result from combination of these materials during manufacture of hard metals, and dusts containing both materials may result from production, finishing, or maintenance (e.g., sharpening or grinding) of cobalt–tungsten carbide hard-metal products. Cobalt–tungsten carbide hard metals are composites of tungsten carbide particles (either alone or in combination with smaller amounts of other carbides) with a metallic cobalt powder as a binder, pressed into a compact, solid form at high temperatures by a process known as "sintering." Cobalt–tungsten carbide hard metals are commonly referred to as "cemented carbides" in the United States, but the term "sintered carbide" also may be used, and some sources refer to cobalt–tungsten carbide products simply as "tungsten carbides" (Brookes 2002).

The physical properties of cobalt–tungsten carbide hard metals vary with the relative proportions of cobalt, tungsten carbide, and other carbides, but they have common properties of extreme hardness, abrasion resistance, and toughness. Tungsten carbide is hard (able to resist cutting, abrasion, penetration, bending, and stretching) but brittle; cobalt is soft but tough (able to withstand great strain without tearing or breaking). The composition of commercial-grade cobalt–tungsten carbide hard metals can vary greatly; it generally ranges from 50% to 97% tungsten carbide (along with other metallic carbides such as titanium carbide or tantalum carbide) and from 3% to 16% cobalt, with variations in grain size and additives. The proportion of cobalt as the binding metal in the composite hard metal depends on the intended use (Azom 2002). Cobalt–tungsten carbide hard metals for various uses have Vickers hardness values (a measure of the resistance of a substance to indentation by a diamond penetrator of special profile) typically ranging from 1250 to 1900 (Brookes 1998).

The crystalline structure of cobalt–tungsten carbide includes the structures individually of cobalt, which can exist as either hexagonal or cubic crystals, and tungsten carbide, which consists primarily of W_2C, WC, and possibly other carbides (Upadhyaya 1998b). The phase diagram for the combination of cobalt and tungsten carbide is extremely complex, as tungsten can form a solid solution in co-

balt, and cobalt can form carbides with carbon; the overall relationship varies with the concentrations of the major components and the temperature.

Mixtures of cobalt and tungsten carbide are more active than the individual components in adsorption of water vapor (with respect to both the amount adsorbed and the interaction energy) and in the catalytic decomposition of hydrogen peroxide (Zanetti and Fubini 1997). Physical and chemical properties of tungsten carbide and cobalt are listed in the following table.

Property	Cobalt	Tungsten carbide
Molecular or atomic weight	58.9	195.9
Density	8.92	15.6
Melting point	1,495°C	2,785°C
Boiling point	2,927°C	6,000°C
Vapor pressure	1 Pa at 1,517°C (0.0075 mmHg)	NR

Source: HSDB 2010. NR = not reported.

Use

About 70% of cobalt–tungsten carbide hard-metal production is used for cutting tools and 30% for wear-resistant materials, primarily for tools for mining and grinding operations (Santhanam 2003). Hard-metal grades for machining are assigned International Organization for Standardization (ISO) codes beginning with "P" for machining of steel, "M" for multiple purposes, including machining of steel, nickel-based superalloys, and ductile cast iron, and "K" for cutting of gray cast iron, nonferrous metals, and nonmetallic materials.

Production

Cobalt–tungsten carbide hard metals were developed in Germany during and after World War I and marketed commercially by a German company in 1927 as Widia, which consisted of tungsten carbide with 6% cobalt as binder (Brookes 1998, Upadhyaya 1998a). Cobalt–tungsten carbide hard-metal manufacturing processes vary somewhat, but all involve production of cobalt and tungsten carbide powders, which are mixed, pressed into a compact, solid form, and sintered by heating to about 1,500°C. The manufacturing process consists of three steps: Step 1, producing the cobalt and tungsten carbide powders; Step 2, mixing, drying, pressing, presintering, shaping the presintered hard metal, and sintering; and Step 3, finishing the sintered products, which includes grinding and sharpening.

Worldwide use of cemented carbides has increased steadily over the years, from about 10 tons in 1930 to 30,000 tons per year in the early 2000s (Azom 2002). In 2004, estimated U.S. production of hard-metal products totaled 5,527 metric tons (6,080 tons) (Hsu 2004). The U.S. Geological Survey (USGS 2008a,b) estimated that 792 metric tons (873 tons) of cobalt (9.3% of total U.S. cobalt consumption) and 6,610 metric tons (7,286 tons) of tungsten (56% of total U.S. tungsten consumption) was used in the production of cemented carbides in the United States in 2007. In 2008, 127 U.S. and Canadian companies were identified that produced or supplied cobalt–tungsten carbide and materials made from cobalt–tungsten carbide (ThomasNet 2008), and the Cemented Carbide Producers Association had 22 U.S. members and partner members (CCPA 2008). In 2007, the United States imported about 1.6 million kilograms (1,800 tons) and exported about 1.3 million kilograms (1,400 tons) of tungsten carbide (USITC 2008); no data specific to U.S. imports or exports of cobalt–tungsten carbide were found.

Exposure

The major source of exposure to cobalt–tungsten carbide powders and hard metals is occupational. However, people who live in the vicinity of hard-metal production or maintenance facilities could be exposed to cobalt–tungsten carbide hard-metal dusts. Although no exposure levels for the general population were found, some studies provided data on possible environmental contamination from the manufacture or maintenance of hard-metal products. Soil sampled from the rear of a cemented carbide tool-grinding plant contained cobalt at concentrations of up to 12,780 mg/kg (Abraham and Hunt 1995). The concentrations of tungsten and cobalt in airborne particulates in Fallon, Nevada, and four nearby towns were characterized by Sheppard *et al.* (2006), who found higher levels of tungsten (0.1 to 40.9 ng/m^3) and cobalt (0.02 to 0.16 ng/m^3) in Fallon than in the other towns. The authors suggested that a hard-metal facility located in Fallon could be a candidate source for airborne exposure to the metals, a suggestion that has been disputed (see NTP 2009).

Sources of occupational exposure to cobalt–tungsten carbide during the manufacture of hard metals include the processes of mixing, drying, pressing, presintering, shaping, and sintering (parts of Step 2, as described under Production) and the processes of grinding and sharpening sintered products (parts of Step 3, as described under Production). Exposure to cobalt–tungsten carbide hard metals can also occur from other miscellaneous manufacturing operations, during processing of hard-metal scrap for recycling, and during end use and maintenance of hard-metal tools. Particle size (and hence respirable fraction), morphology, and concentrations of airborne dusts and bulk dusts were found to differ among production areas (Stefaniak *et al.* 2007). For cobalt-containing particles, the minimum mass median aerodynamic diameter (MMAD) was 6 μm (for dry grinding), and the maximum MMAD was over 18 μm (for scrap reclamation and pressing operations); the MMAD for powder mixing was around 10 μm, which is generally considered the maximum diameter for respirable particles in humans. Inhalable, thoracic, and respirable particles were found in all work areas of three facilities that together carried out the cobalt–tungsten carbide manufacturing process, with the highest levels reported for the powder-mixing area (Stefaniak *et al.* 2009). Cobalt and tungsten have been detected in workers' urine, blood, hair, toenails, and bronchoalveolar lavage fluid, and through open lung and transbronchial biopsy (NTP 2009).

Step 2 processes, particularly powder-processing operations, generally are associated with the highest airborne exposures; several studies reported cobalt concentrations approaching or exceeding 5,000 μg/m^3 (NTP 2009). A maximum mean cobalt air concentration of 32,740 μg/m^3 (range = 44 to 438,000 μg/m^3) was reported during weighing and mixing operations in a U.S. manufacturing facility (Sprince *et al.* 1984). An Italian study reported a mean tungsten air concentration of 26 μg/m^3 (Sabbioni *et al.* 1994a), and a German study reported a maximum single measurement of 254 μg/m^3 (Kraus *et al.* 2001). Among workers involved in Step 2 manufacturing processes, cobalt was detected in the urine (at up to 2,100 μg/L), blood or serum (at up to 32 μg/L), and hair (at up to 25.8 ppm), and tungsten was detected in urine (at up to 169 μg/L).

Cobalt air concentrations reported for Step 3 processes (including tool finishing, grinding, and reconditioning operations) have generally been lower than those for Step 2, but have exceeded 1,000 μg/m^3 in some studies (NTP 2009). For Step 3 processes, a maximum mean cobalt air concentration of 1,292 μg/m^3 and a maximum single measurement of 2,440 μg/m^3 were reported, both for dry-grinding operations. For tungsten in air, a maximum mean concentration of 5,160 μg/m^3 and a maximum single measurement of 12,800 μg/m^3 were reported. Among workers involved specifically in Step 3 processes, cobalt was detected in urine (at up to 730 μg/L), blood (at up to 39 μg/L), and hair (at up to 9.11 ppm). Tungsten also was detected in urine (at up to 1,000 μg/L) and blood (at up to 60 μg/L).

A few studies reported on exposure for jobs outside of the cobalt–tungsten carbide production process. McDermott (1971) reported airborne cobalt concentrations during packing operations (10 to 250 μg/m^3), equipment cleaning (40 to 820 μg/m^3), and miscellaneous operations (10 to 6,700 μg/m^3), but the nature of these operations was not defined further. Maintenance activities (including housekeeping) were reported by Scansetti *et al.* (1985) to result in airborne cobalt concentrations exceeding 50 μg/m^3, and Kraus *et al.* (2001) reported urinary levels associated with maintenance activities ranging from 1.3 to 4.7 μg/L for cobalt and 1.5 to 5.3 μg/L for tungsten.

Information on exposure from the end use of hard-metal tools is limited; however, exposure appears to be minimal. Pellet *et al.* (1984, as cited in Angerer and Heinrich 1988) reported cobalt air concentrations of 180 to 193 μg/m^3 and a mean urinary cobalt concentration of 11.7 μg/L associated with use of hard metal; however, no additional information was provided for these data. No other information was found that directly demonstrated exposure to cobalt–tungsten carbide powders and hard metals by end users of products containing the material. The Washington State Department of Labor, in a Hazard Alert issued in March 1995, stated that there was no evidence of substantial exposure to cobalt during the use of tools containing tungsten carbide or other hard metals (WSDLI 1995).

Several studies found significant correlations between cobalt concentrations in air and in workers' blood or urine (Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994b). Urinary cobalt levels for hard-metal workers have been reported to increase through the workday (Torra *et al.* 2005) and workweek (Lison *et al.* 1994, Scansetti *et al.* 1998, Torra *et al.* 2005). In one study, urinary cobalt concentrations were significantly higher ($P < 0.005$) at the end of a shift than at the beginning of the shift, with significant increases "day in and day out" during the workweek (Torra *et al.* 2005).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Water Act

Tungsten and cobalt discharge limits are imposed for numerous processes during the production of tungsten or cobalt at secondary tungsten and cobalt facilities processing tungsten or tungsten carbide scrap raw materials.

Discharge limits for tungsten are imposed for numerous processes during the production of tungsten at primary tungsten facilities.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limits (PEL) (8-h TWA) = 0.1 mg/m^3 for cobalt metal, dust, and fume (as Co); = 5 mg/m^3 for insoluble tungsten compounds (as W).

Short-term exposure limits (STEL) = 10 mg/m^3 for insoluble tungsten compounds (as W).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m^3 for cobalt and inorganic cobalt compounds; = 5 mg/m^3 for tungsten metal and insoluble compounds.

Threshold limit value – short-term exposure limit (TLV-STEL) = 10 mg/m^3 for tungsten metal and insoluble compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 15 μg/L for cobalt in urine; = 1 μg/L for cobalt in blood.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m^3 for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m^3 for cobalt metal dust and fume (as Co); = 5 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m^3 for cobalt metal dust and fume (as Co).

Short-term exposure limit (STEL) = 10 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

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Coke-Oven Emissions

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Carcinogenicity

Coke-oven emissions are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Before 1950, numerous case reports linked employment in coke production with cancer of the skin, urinary bladder, and respiratory tract. Since then, several cohort studies conducted in the United States, the United Kingdom, Japan, and Sweden have reported an increased risk of lung cancer in humans exposed to coke-oven emissions. Smoking was accounted for in some of these studies and was not found to be a significant confounding factor. A large cohort study of 59,000 steel workers published in 1969 reported that lung-cancer risk increased

with increasing duration or intensity of exposure to coke oven fumes. Several studies of coking-plant workers reported an increased risk of kidney cancer. An excess of cancer at other tissue sites (prostate, large intestine, and pancreas) was reported in no more than one study for each site (IARC 1984, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of coke-oven emissions from studies in experimental animals. Exposure to coke-oven emissions caused tumors in two rodent species, at two different tissue sites, and by two different routes of exposure. Coke-oven emission samples applied weekly to the skin of mice for up to 52 weeks caused skin cancer, and these samples also showed tumor-initiating activity in initiation-promotion studies in mice. In several studies, inhalation exposure to coal-tar aerosols generated from samples collected from coke ovens caused benign and malignant lung tumors in rats and mice and skin tumors in female mice (IARC 1984).

Studies on Mechanisms of Carcinogenesis

Chemical analyses of coke-oven emissions revealed the presence of numerous known carcinogens and potentially carcinogenic chemicals, including several polycyclic aromatic hydrocarbons (PAHs), nitrosamines, coal tar, arsenic compounds, and benzene. In addition, coke-oven emissions contain several agents known to enhance the effect of chemical carcinogens, especially on the respiratory tract (IARC 1984).

Properties

Coke is produced by blending and heating bituminous coals to 1,000°C to 1,400°C in the absence of oxygen. Tars and light oils are distilled out of the coal, and gases are generated during this process. Coke-oven emissions are defined as the benzene-soluble fraction of total particulate matter generated during coke production. These emissions are complex mixtures of dusts, vapors, and gases that typically include PAHs, formaldehyde, acrolein, aliphatic aldehydes, ammonia, carbon monoxide, nitrogen oxides, phenol, cadmium, arsenic, and mercury. More than 60 organic compounds, including more than 40 PAHs, have been identified in air samples collected at coke plants. One metric ton of coal yields approximately 545 to 635 kg (1,200 to 1,400 lb) of coke, 45 to 90 kg (100 to 200 lb) of coke breeze (large coke particulates), 7 to 9 kg (15 to 20 lb) of ammonium sulfate, 27.5 to 34 L (7.3 to 9.8 gal) of coke oven gas tar, 55 to 135 L (14.5 to 35.7 gal) of ammonia liquor, and 8 to 12.5 L (2.1 to 3.3 gal) of light oil. About 20% to 35% of the initial coal charge is emitted as gases and vapors, most of which are collected in by-product coke production. Coke-oven gas includes hydrogen, methane, ethane, carbon monoxide, carbon dioxide, ethylene, propylene, butylene, acetylene, hydrogen sulfide, ammonia, oxygen, and nitrogen. Coke-oven gas tar includes pyridine, tar acids, naphthalene, creosote oil, and coal-tar pitch. Benzene, xylene, toluene, and solvent naphthas may be extracted from the light-oil fraction (IARC 1984).

Use

The primary use of coke is as a fuel reductant and support for other raw materials in iron-making blast furnaces. Coke is also used to synthesize calcium carbide and to manufacture graphite and electrodes, and coke-oven gas is used as a fuel. By-products of coke production may be refined into commodity chemicals (such as benzene, toluene, naphthalene, sulfur, and ammonium sulfate) (IARC 1984, Kaegi *et al.* 2000).

Production

Coke production in the United States increased steadily between 1880 and the early 1950s, peaking at 72 million tons in 1951. In 1976, the United States ranked second in the world in coke production, producing 52.9 million tons, or about 14.4% of world production (Kaegi *et al.* 2000). In 1990, U.S. production was 27 million tons, fourth highest worldwide. Production gradually declined from 22 million tons in 1997 to 16.8 million tons in 2002 (EIA 2003). Demand for blast-furnace coke declined because technological improvements reduced the amount of coke consumed per amount of iron produced by 10% to 25% (Kaegi *et al.* 2000). However, annual consumption from 1997 to 2002 exceeded production by 1 million to 3 million tons. Thus, for this period, U.S. imports (2.5 million to 3.8 million tons) consistently exceeded exports (0.8 to 1.3 million tons).

In 1984, it was estimated 330,000 lb to 3.5 million pounds of coke-oven emissions was produced annually in the United States (CEN 1984). Although the by-product process is designed to collect the volatile materials given off during the coking process, emissions escape because of structural defects around the doors or charging lids, improper use of engineering controls, improper work practices, and insufficient engineering controls (IARC 1984).

Exposure

The primary routes of potential human exposure to coke-oven emissions are inhalation and dermal contact. Occupational exposure may occur during the production of coke from coal or the use of coke to extract metals from ores, to synthesize calcium carbide, or to manufacture graphite and electrodes. Workers at coking plants and coal tar production plants, as well as people who live near these plants, have a high risk of possible exposure to coke-oven emissions. In 1970, the United States had 64 coking plants operating more than 13,000 coke ovens, with an estimated 10,000 coke-oven workers potentially exposed to coke-oven emissions (NIOSH 1973). The numbers of plants and ovens remained essentially the same through 1975 but by 1998 had declined to 23 coking plants operating about 3,800 ovens (EPA 2001). During the past several decades, pollution-control efforts have reduced coke-oven emissions (Costantino *et al.* 1995, Kaegi *et al.* 2000).

About 60% of total coke-oven emissions occur during charging, 30% during pushing, and 10% during quenching of the coke (Kaegi *et al.* 2000). A study reported measurements of exposure of employees to coke-oven emissions (average breathing-zone concentration) at a steel plant from 1979 to 1983, by job classification. The exposure levels depended on depended on proximity to the oven during the coking process (Keimig *et al.* 1986). Exposure levels were highest for larry-car operator, lidman, and door-machine operator; intermediate for benchman–coke side and benchman–pusher side; and lowest for pusher operator, quencher-car operator, heater, and heater helper. Data compiled by the International Agency for Research on Cancer (IARC 1984) indicated that average concentrations of coke-oven emissions in the breathing zones of workers were lowest for pusher-machine operator (0.39 mg/m^3) and highest for lidman (3.22 mg/m^3), tar chaser (3.14 mg/m^3), and larry-car operator (3.05 mg/m^3).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.15 mg/m^3 for the benzene-soluble fraction.

Comprehensive standards for occupational exposure to coke-oven emissions have been developed.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.2 mg/m^3 for the benzene-soluble fraction.

Listed as a potential occupational carcinogen.

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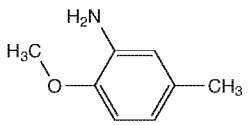
p-Cresidine

CAS No. 120-71-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

p-Cresidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *p*-cresidine caused tumors at several different tissue sites in mice and rats. Dietary administration of *p*-cresidine caused cancer of the urinary bladder (carcinoma, including squamous- and transitional-cell carcinoma) in mice and rats of both sexes, nasal cancer (olfactory neuroblastoma) in rats of both sexes, liver cancer (hepatocellular carcinoma) in female mice, and benign liver tumors (adenoma) in male rats (NCI 1979).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to *p*-cresidine.

Properties

p-Cresidine is an aromatic amine that exists as white crystals at room temperature. It is slightly soluble in water and chloroform and soluble in ethanol, ether, benzene, and petroleum ether (HSDB 2009). Physical and chemical properties of *p*-cresidine are listed in the following table.

Property	Information
Molecular weight	137.2[a]
Density	1.0 g/cm^3 at 20°C[b]
Melting point	52°C[a]
Boiling point	235°C[a]
Log K_{ow}	1.74[a]
Water solubility	2.81 g/L at 25°C[c]
Vapor pressure	2.52×10^{-2} mm Hg at 25°C[c]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

p-Cresidine is used exclusively as a synthetic chemical intermediate to produce azo dyes and pigments, such as FD&C red no. 40 and C.I. direct black 17, direct blue 67, direct blue 126, direct green 26, direct orange 34, direct orange 83, direct red 79, direct violet 51, direct yellow 41, disperse black 2, direct orange 72, and direct violet 9. The dyes made with *p*-cresidine have been produced commercially in the United States and are used in the food and textile industries (NCI 1979, IARC 1982).

Production

p-Cresidine has been produced in the United States since 1926 (IARC 1982). In 2009, *p*-cresidine was produced by one manufacturer each in the United States and Europe and two manufacturers in India (SRI 2009) and was available from 26 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports were found specifically for *p*-cresidine. Reports filed in 1986, 1990, and 1994 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *p*-cresidine totaled 1 million to 10 million pounds. The reported quantities were 500,000 lb to 1 million pounds in 1998 and 10,000 to 500,000 lb in 2002 (EPA 2004). In 2006, the quantity was less than 500,000 lb (EPA 2009).

Exposure

The routes of potential human exposure to *p*-cresidine are inhalation, ingestion, and dermal contact (HSDB 2009). *p*-Cresidine has been identified as a contaminant in FD&C red dye no. 40, which is used in gelatins, puddings, dairy products, confections, beverages, and condiments (FoodAdditives 2006, Richfield-Fratz *et al.* 1989). EPA's Toxics Release Inventory reported that in 1988, almost 13,000 lb of *p*-cresidine was released, mostly to air. From 1988 to 2002, environmental releases declined steadily except in 2000, when slightly over 12,000 lb was released to an off-site waste broker. No releases of *p*-cresidine were reported from 2002 to 2004. After 2004, releases of 260 lb (250 lb to surface water and 10 lb to air) were reported in 2005, 2006, and 2007 (TRI 2009). When released to air, *p*-cresidine is expected to exist solely as a vapor, with an estimated half-life of 2 hours. It is volatile in water, with an estimated half-life of 23 days in a river model and 169 days in a lake model. When released to soil or water, it is expected to bind to organic matter in soil, sediment,

or suspended solids, because of the reactivity of the aromatic amine group. It is not expected to hydrolyze rapidly or to bioaccumulate in aquatic organisms (HSDB 2009).

Potential occupational exposure is believed to have been limited to workers in dye-production facilities in the past (NCI 1979). No estimates were found of the number of workers potentially exposed to *p*-cresidine.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

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NCI. 1979. *Bioassay of p-Cresidine for Possible Carcinogenicity (CAS No. 120-71-8).* Technical Report Series No. 142. DHEW (NIH) Publication No. 78-1394. Bethesda, MD: National Institutes of Health. 63 pp.

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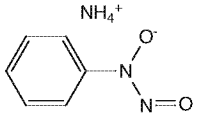
TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer and select *p*-cresidine. Last accessed: 7/21/09.

Cupferron

CAS No. 135-20-6

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Cupferron is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to cupferron caused tumors at several different tissue sites in mice and rats. Dietary administration of cupferron caused blood-vessel cancer (hemangiosarcoma or hemangioma) in rats and mice of both sexes and liver cancer (hepatocellular carcinoma) in rats of both sexes and in female mice (NCI 1978). It also caused cancer of the skin of the ear (carcinoma of the auditory sebaceous gland) in female rats and mice, cancer of the forestomach (squamous-cell carcinoma) in rats of both sexes, and benign tumors of the Harderian gland (adenoma) in female mice.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to cupferron.

Properties

Cupferron is the ammonium salt of *N*-nitroso-*N*-phenylhydroxylamine and exists as a creamy-white crystalline solid at room temperature. It is soluble in water, alcohol, and ether (ChemIDplus 2009, HSDB 2009). Cupferron can produce irritating, corrosive, or toxic gases as combustion products (Akron 2009). Physical and chemical properties of cupferron are listed in the following table.

Property	Information
Molecular weight	155.2[a]
Melting point	163°C to 164°C[a]
Log K_{ow}	–1.73[b]
Water solubility	608 g/L at 25°C[b]
Vapor pressure	6.29×10^{-5} mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Cupferron is an analytical reagent that complexes with metal ions and is used to separate and precipitate metals such as copper, iron, vanadium, and thorium. It is used to separate tin from zinc and to separate copper and iron from other metals. In analytical laboratories, cupferron is a reagent used for quantitative determination of vanadates and titanium and the colorimetric determination of aluminum (NCI 1978, HSDB 2009).

Production

In 2009, cupferron was produced by one manufacturer in East Asia and four manufacturers in India (SRI 2009) and was available from 28 suppliers, including 17 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of cupferron were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule every four years from 1986 to 2002 (except in 1994) indicated that U.S. production plus imports of cupferron totaled 10,000 to 500,000 lb (EPA 2004).

Exposure

The primary routes of potential human exposure to cupferron are ingestion and inhalation of the dust of the dry salt. Dermal contact is a secondary route of potential exposure (HSDB 2009). According to EPA's Toxics Release Inventory, the largest reported environmental releases of cupferron since 1988 were of 1,500 lb in 1989 and 1,200 lb in 1991, mostly to air. No releases were reported from 1995 to 1999, and the last year for which releases were reported was 2000, when 343 lb was released to surface water. In 2007, one industrial facility was listed as using cupferron; however, no releases were reported (TRI 2009). The potential for exposure appears to be greatest among individuals engaged in analytical or research studies involving the use of cupferron. Workers may also potentially be exposed during manufacturing processes (NCI 1978). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 136 workers (in the Primary Metal industries), including 39 women, potentially were exposed to cupferron (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

References

Akron. 2009. *The Chemical Database*. The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 5/09.

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EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. http://www.epa.gov/oppt/iur/tools/data/2002-vol.html and search on CAS number.

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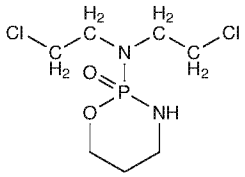
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. http://www.epa.gov/triexplorer and select Cupferron. Last accessed: 5/09.

Cyclophosphamide

CAS No. 50-18-0

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Cyclophosphamide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Several epidemiological studies consistently found excesses of urinary-bladder cancer and leukemia among people treated with cyclophosphamide for various medical conditions. A case-control study in Germany found that the risk of leukemia increased with increasing dose of cyclophosphamide (IARC 1981, 1987). More recently, a nested case-control study of non-Hodgkin's lymphoma patients reported that the risk of urinary-bladder cancer increased with increasing cumulative dose of cyclophosphamide (Travis *et al.* 1995).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of cyclophosphamide from studies in experimental animals. Exposure to cyclophosphamide caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure (IARC 1981). In rats, exposure to cyclophosphamide in drinking water or by intravenous injection caused benign and malignant tumors at various tissue sites, including the urinary bladder. Cyclophosphamide administered by intraperitoneal injection to female rats caused benign and malignant mammary-gland tumors. In mice, cyclophosphamide administered by subcutaneous or intraperitoneal injection caused leukemia, lymphoma, and benign and malignant tumors at various sites, including the lung, liver, mammary gland, and injection site (IARC 1981, 1987).

Properties

Cyclophosphamide is an antineoplastic and immunosuppressant agent that is usually a fine white crystalline powder at room temperature. The substance liquefies and becomes an oily semisolid mass when water is removed under high vacuum. It is soluble in water, alcohol, chloroform, dioxane, and glycols, slightly soluble in benzene and carbon tetrachloride, very slightly soluble in ether and acetone, and insoluble in carbon disulfide. Cyclophosphamide is sensitive to oxidation, moisture, and light (Akron 2009). Physical and chemical properties of cyclophosphamide are listed in the following table.

Property	Information
Molecular weight	261.1[a]
Density	1.479 g/cm^3[b]
Melting point	49.5°C to 53°C[a]
Boiling point	336°C [b]
Log K_{ow}	0.63[a]
Water solubility	40 g/L at 20°C[a]
Vapor pressure	4.45×10^{-5} mm Hg at 25°C[c]
Dissociation constant (pK_b)	9.91[b]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

Cyclophosphamide is used as a drug to treat cancer and other medical conditions. In chemotherapy, it may be used alone, but more frequently is used concurrently or sequentially with other anticancer drugs. Cyclophosphamide is available in the United States as 25- or 50-mg tablets, as an oral solution, or in a crystalline hydrate form for injection in strengths of 100 to 2,000 mg. It is used to treat malignant lymphoma, multiple myeloma (bone-marrow cancer), leukemia, breast and ovarian cancer, neuroblastoma (childhood nerve-cell cancer), retinoblastoma (childhood cancer of the retina), and mycosis fungoides (lymphoma of the skin) (MedlinePlus 2009, RxList 2010). Cyclophosphamide is also used as an immunosuppressive agent following organ transplants or to treat autoimmune disorders such as rheumatoid arthritis, Wegener's granulomatosis (an inflammation of the blood vessels), and nephrotic syndrome (a kidney disorder) in children (Chabner *et al.* 2001). Researchers have tested cyclophosphamide for use as an insect chemosterilant and in the chemical shearing of sheep (IARC 1975).

Production

Cyclophosphamide is not produced in the United States, and no data on U.S. imports were found. Total U.S. sales were 600 kg (1,300 lb) annually in the mid 1970s (IARC 1975); more recent data were not found. In 2009, cyclophosphamide was available from seven U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing cyclophosphamide as the active ingredient were produced by eleven U.S. pharmaceutical companies (FDA 2009).

Exposure

The general population is not expected to be exposed to cyclophosphamide, because its use is limited to medical treatment. An estimated 500,000 patients worldwide are treated with cyclophosphamide annually (Travis *et al.* 1995). Doses used in medical treatment depend on the patient and the specific disease. Cyclophosphamide may be given orally (in 25- or 50-mg tablet form) or by intravenous injec-

tion (from 100-, 200-, or 500-mg or 1- or 2-g vials) (FDA 2009). The initial treatment for cancer patients with no hematologic deficiency may be 40 to 50 mg/kg of body weight in divided intravenous doses over two to five days; other regimens are 10 to 15 mg/kg every seven to ten days or 3 to 5 mg/kg twice a week. The adult dosage for tablets typically is 1 to 5 mg/kg per day for both initial and maintenance treatment of cancer. For nonmalignant diseases, an oral dose of 2.5 to 3 mg/kg per day is administered for 60 to 90 days (RxList 2010). In 2009, 1,564 clinical trials using cyclophosphamide were in progress or recently completed (ClinicalTrials 2009).

Occupational exposure may occur from skin contact or inhalation of dust during drug formulation or packaging. Health professionals who handle cyclophosphamide, such as pharmacists, nurses, and physicians, could potentially be exposed during drug preparation, administration, or cleanup; however, exposure can be avoided through the use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981). In a cross-sectional study of hospital workers, handling of cyclophosphamide was clearly related to its detection in the urine (Evelo *et al.* 1986). Of 62 urine samples collected from 17 nurses and pharmacy technicians who prepared or administered antineoplastic drugs, including cyclophosphamide, 18 contained cyclophosphamide, at concentrations ranging from 50 ng/L (the limit of detection) to 10,030 ng/L. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 30,026 workers, including 20,745 women, potentially were exposed to cyclophosphamide (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of cyclophosphamide = U058.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Cyclophosphamide is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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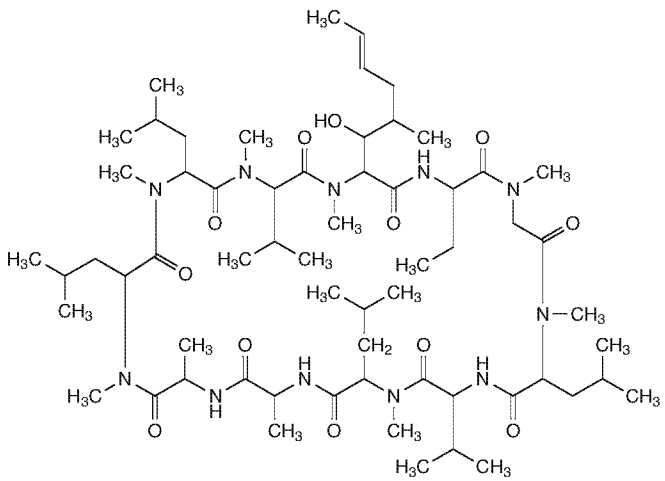
Cyclosporin A

CAS No. 59865-13-3

Known to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as ciclosporin or cyclosporine



Carcinogenicity

Cyclosporin A is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports describe cancer (mainly lymphoma, Kaposi's sarcoma, or skin cancer) developing in organ-transplant recipients, psoriasis patients, and rheumatoid arthritis patients treated with cyclosporin A as an immunosuppressive agent. Some of these patients were treated with cyclosporin A alone, whereas others were treated with other immunosuppressive agents in combination with cyclosporin A. The time between the start of treatment and development of tumors ranged from 1 month to 10 years. In some cases, tumors regressed after treatment with cyclosporin A was discontinued.

Several epidemiological studies (cohort studies) also indicate that cyclosporin A is carcinogenic in humans, causing tumors at an incidence of less than 5% in the patient population (IARC 1990).

Cancer Studies in Experimental Animals

Cyclosporin A administered in the diet of mice for 78 days (at doses of up to 16 ppm) or in the diet of rats for 95 to 105 weeks (at doses of up to 8 mg/kg of body weight) did not cause tumors at any tissue site. However, when male mice of a strain with a high spontaneous rate of thymus cancer (thymic lymphoma) were fed a diet containing a high dose of cyclosporin A (150 ppm) for 20 to 34 weeks, the incidence of this cancer was increased (IARC 1990). When rats with streptozotocin-induced diabetes were administered cyclosporin A in the diet at 10 mg/kg of body weight for 20 weeks, more than half developed kidney tumors; however, the incidence of these tumors in control animals was not reported (Reddi *et al.* 1991). Macaque monkeys that had received heart or heart-lung transplants (allografts) were administered cyclosporin A alone or in combination with other immunosuppressive agents, by intramuscular injection. The incidence of lymphoma (a rare neoplasm in macaques) was increased in these monkeys, but not in grafted monkeys treated with immunosuppressive regimens that did not include cyclosporin A (IARC 1990).

Studies on Mechanisms of Carcinogenesis

In tumor initiation-promotion studies, cyclosporin A increased the incidence of lymphoid tumors in male mice exposed either to radiation or *N*-methyl-*N*-nitrosourea (MNU), hepatocellular carcinoma in male rats initiated with diethylnitrosamine, and intestinal adenocarcinoma in male rats administered MNU (IARC 1990, Masuhara *et al.* 1993). Cyclosporin A also increased the incidence of cervical lymph node metastasis in hamsters exposed to dimethylbenz[*a*]anthracene (Yamada *et al.* 1992) and metastasis of tumors to the liver in male mice inoculated via the portal vein with MCA 38 colon tumor cells (Yokoyama *et al.* 1994) or colon-26 tumor cells (Suzaki *et al.* 1995). In contrast, cyclosporin A did not increase the incidence of adenoma in male mice exposed to urethane, in male rats initiated with 3-methylcholanthrene, or in rats exposed to *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (IARC 1990, Bussiere *et al.* 1991).

Cyclosporin A did not cause genetic damage in a number of test systems, including gene mutation in prokaryotes, gene mutation or chromosomal aberrations in cultured mammalian cells, chromosomal aberrations or micronucleus formation in rodent bone-marrow cells, DNA repair in mouse testicular cells, or dominant lethal mutation in male mice (IARC 1990, Zwanenburg and Cordier 1994). However, cyclosporin A did cause sister chromatid exchange in human lymphocytes *in vitro* and unscheduled DNA synthesis and chromosomal aberrations in the peripheral blood lymphocytes of kidney-transplant patients treated with cyclosporin A and prednisolone (IARC 1990).

The most likely explanation for the increased incidence of tumors in patients treated with cyclosporin A is immune suppression (Ryffel 1992).

Properties

Cyclosporin A is an immunosuppressive agent that is a cyclic nonpolar oligopeptide composed of 11 amino acid residues. It is a white crystalline solid at room temperature and is slightly soluble in water and saturated hydrocarbons, very soluble in acetone, diethyl ether, and methanol, and soluble in chloroform. It is sensitive to light, cold, and oxidation (IARC 1990). Physical and chemical properties of cyclosporin A are listed in the following table.

Property	Information
Molecular weight	1203[a]
Melting point	148°C to 151°C[a]
Log K_{ow}	2.92[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Cyclosporin A has been used as an immunosuppressive agent since the mid 1980s. It is used extensively in the prevention and treatment of graft-versus-host reactions in bone-marrow transplantation and to prevent rejection of kidney, heart, and liver transplants. It is also used as an ophthalmic emulsion for the topical treatment of dry eye syndrome. In addition, it has been tested for use as therapy for a large variety of other diseases in which immunological factors may have a pathogenetic role, including Graves' disease, uveitis, Crohn's disease, ulcerative colitis, chronic active hepatitis, primary biliary cirrhosis, diabetes mellitus, myasthenia gravis, sarcoidosis, dermatomyositis, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and certain nephropathies (IARC 1990, Reents 1996). Cyclosporin A is used alone or in combination with azathioprine, prednisolone, prednisone, antilymphocyte globulin, actinomycin, cyclophosphamide, methylprednisolone, or phototherapy (e.g., PUVA, UVB). Cyclosporin A is administered orally, intravenously, or topically. Oral preparations may contain corn, castor, or olive oil in ethanol; intravenous preparations contain 33% alcohol and a castor-oil vehicle; and topical preparations may contain glycerin, castor oil, polysorbate 80, carbomer 1342, and sodium hydroxide. A microemulsion oral formula of cyclosporin A was approved by the U.S. Food and Drug Administration in 1995 (Reents 1996).

Production

Cyclosporin A may be biosynthesized by the fungus *Tolypocladium inflatum* or may be produced synthetically. It is manufactured commercially in Europe and East Asia (SRI 2009). In 2009, 20 U.S. suppliers of cyclosporin A were identified (Chem Sources 2009), and FDA-approved drug products containing cyclosporin A as the active ingredient were produced by 11 U.S. pharmaceutical companies (FDA 2009). No data on U.S. imports or exports of cyclosporin A were found.

Exposure

The primary routes of potential human exposure to cyclosporin A are intravenous and oral administration. Patients receiving immunosuppressive therapy for organ transplants, rheumatoid arthritis, and other diseases may be exposed to cyclosporin A. Cyclosporin A is available in oral capsules (25, 50, or 100 mg), 100-mg/mL oral solutions, 0.05% ophthalmic emulsions, and 50-mg/mL injectable vials (FDA 2009). In 2008, sales of one brand-name product with cyclosporin A as the active ingredient totaled over $339 million, with over 2 million prescriptions filled, and sales of generic cyclosporin A totaled $56 million (DrugTopics 2009a,b,c). A typical oral dosage of cyclosporin A is 18 mg/kg of body weight daily, beginning 12 hours before transplantation and continuing for one to two weeks, followed by reduction of the dosage to 5 to 10 mg/kg or less. Cyclosporin A may also be given intravenously at one third the oral dose. This drug often is given to transplant recipients for several months (IARC 1990). Occupational exposure potentially may occur among workers formulating or packaging the solutions and health-care professionals administering the drug.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Cyclosporin A is a prescription drug subject to specific labeling requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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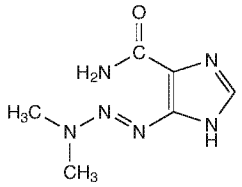
Dacarbazine

CAS No. 4342-03-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Dacarbazine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dacarbazine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. It caused cancer of the mammary gland (adenocarcinoma), spleen (lymphosarcoma), and thymus (lymphosarcoma) in male and female rats following dietary exposure and in female rats following intraperitoneal injection. It also caused brain tumors (cerebral ependymoma) in female rats following dietary exposure. Tumors occurred as soon as 18 weeks after the start of dietary exposure. In mice, intraperitoneal injection of dacarbazine caused lung tumors in both sexes, lymphoma and blood-vessel tumors (hemangioma in the spleen) in males, and uterine tumors in females (IARC 1981).

Since dacarbazine was listed in the *Fourth Annual Report on Carcinogens,* an additional study in rodents has been identified. Prenatal exposure to dacarbazine caused tumors in rats, predominantly cancer of the peripheral nerves (malignant neurinoma) (IARC 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dacarbazine. A retrospective cohort study of Hodgkin's disease patients treated with various types of combination chemotherapy or radiotherapy evaluated records from 1,032 consecutive patients from 1965 to 1978. No secondary cases of solid tumors or acute non-lymphoblastic leukemia occurred in the subpopulation of patients treated with dacarbazine plus adriamycin, bleomycin, and vinblastine (ABVD therapy) alone or in combination with radiotherapy; however, the number of patients treated with ABVD therapy was small (Valagussa *et al.* 1980, 1982, IARC 1981, 1987).

Since dacarbazine was listed in the *Fourth Annual Report on Carcinogens,* another study of Hodgkin's disease patients has been identified, which found no increased risk of acute leukemia among patients treated with ABVD therapy alone or in combination with nonalkylating chemotherapeutic drugs (Brusamolino *et al.* 1998).

Properties

Dacarbazine is a triazene prodrug with alkylating (methylating) properties. It exists at room temperature as a white to ivory-colored microcrystalline substance. It is slightly soluble in water and is stable in neutral solutions when stored in the dark. However, it decomposes rapidly to 4-diazoimidazole-5-carboxamide when exposed to light, and it decomposes explosively at high temperatures (250°C to 255°C) (IARC 1981). Physical and chemical properties of dacarbazine are listed in the following table.

Property	Information
Molecular weight	182.2[a]
Melting point	205°C[a]
Log K_{ow}	0.24[a]
Water solubility	4.22 g/L at 25°C[b]
Vapor pressure	2.2×10^{-8} mm Hg at 25°C[b]
Dissociation constant (pK_a)	4.42[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Dacarbazine has been used as an antineoplastic agent since the early 1970s, usually in combination regimens. Dacarbazine is used in the treatment of malignant melanoma, Hodgkin's disease, neuroblastoma, osteogenic sarcoma, malignant glucagonoma, and soft-tissue sarcoma, such as leiomyosarcoma, fibrosarcoma, and rhabdomyosarcoma. It is occasionally used in therapy for other neoplastic diseases that have become resistant to alternative treatments (IARC 1981, MedlinePlus 2003).

Production

Dacarbazine is not reported to be produced in the United States. In 2009, it was produced by one manufacturer in China and one in Europe (SRI 2009) and was available from one supplier worldwide, in the United States (ChemSources 2009). Volumes of U.S. imports of dacarbazine have not been reported (IARC 1981). In 2009, nine drug products containing dacarbazine as the active ingredient were produced by five manufacturers (FDA 2009).

Exposure

Dacarbazine is available as an injectable solution in 100-, 200-, and 500-mg vials (FDA 2009). The typical initial dose is 2 to 4.5 mg/kg of body weight per day intravenously or intra-arterially for 10 days, repeated every 4 weeks, or 100 to 250 mg/m^2 of body surface area for 5 days, repeated every 3 weeks (IARC 1981). Health professionals and support staff, such as pharmacists, nurses, physicians, and custodians, may be exposed to dacarbazine by dermal contact, inhalation, or accidental ingestion during drug preparation, or administration or cleanup of medical waste, including excretions of patients treated with dacarbazine (Zimmerman *et al.* 1981, NIOSH 2004). Workers involved in formulation or packaging of dacarbazine drug products may also be exposed. In humans, about half of the drug is excreted unchanged in the urine (Chabner *et al.* 2001). The risks from occupational exposure can be avoided through use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981).

Regulations

Food and Drug Administration (FDA)

Dacarbazine is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Zimmerman PF, Larsen RK, Barkley EW, Gallelli JF. 1981. Recommendations for the safe handling of injectable antineoplastic drug products. *Am J Hosp Pharm* 38(11): 1693-1695.

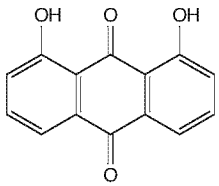
Danthron

CAS No. 117-10-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 1,8-dihydroxyanthraquinone or chrysazin



Carcinogenicity

Danthron is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to danthron caused tumors in two rodent species and at several different tissue sites. Dietary administration of danthron caused liver cancer (hepatocellular carcinoma) in male mice and benign and malignant intestinal-tract tumors (adenoma and adenocarcinoma of the colon and adenoma of the cecum) in male rats (IARC 1990).

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to danthron. One case report was identified that described the occurrence of cancer of the small intestine (leiomyosarcoma) in an

18-year-old girl with a history of prolonged exposure to danthron (Patel *et al.* 1989).

Studies on Mechanisms of Carcinogenesis

Danthron has been evaluated for its ability to promote the induction of tumors by other chemicals. When danthron was fed to male mice that also received 1,2-dimethylhydrazine as a tumor initiator, the incidence and multiplicity of colon tumors (adenoma or adenocarcinoma) and liver tumors (adenoma) were significantly increased (Sugie *et al.* 1994). However, danthron did not promote the induction of tumors when either painted on the skin of mice pretreated with 7,12-dimethylbenz[*a*]anthracene or fed to rats pretreated with 1,2-dimethylhydrazine (IARC 1990). Danthron was found to cause genetic damage in a limited number of *in vitro* test systems, including *Salmonella typhimurium*, yeast, and mammalian cell cultures (IARC 1990).

Properties

Danthron is an anthraquinone that exists at room temperature as a reddish or orange crystalline powder. It is practically insoluble in water, soluble in acetone, chloroform, diethyl ether, and ethanol, and very soluble in alkaline hydroxide solutions (IARC 1990). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of danthron are listed in the following table.

Property	Information
Molecular weight	240.2[a]
Specific gravity	1.54 g/cm^3[b]
Melting point	193°C[a]
Boiling point	sublimes[b]
Log K_{ow}	3.94[a]
Water solubility	9 mg/L[a]
Vapor pressure	7.6×10^{-11} mm Hg[a]
Vapor density relative to air	8.3[b]

Sources: [a]ChemIDplus 2009, [b]Akron 2009.

Use

Danthron has been used since the beginning of the twentieth century as a laxative (IARC 1990). In 1987, U.S. manufacturers voluntarily withdrew production of human drug products containing danthron, and in 1999, the U.S. Food and Drug Administration issued the final rule ordering the withdrawal of danthron-containing products from the U.S. market for use as laxatives (FDA 1999). However, danthron has continued to be used as a pharmaceutical in the United Kingdom (Bennett and Cresswell 2003). To a lesser extent, danthron has been used as an intermediate in the manufacture of alizarine and indanthrene dyes (Akron 2009).

Production

In the past, danthron was synthesized in Germany, India, Japan, Poland, the United Kingdom, and the United States (IARC 1990). In 2009, danthron was produced by one manufacturer in Europe and two manufacturers in China (SRI 2009) and was available from 24 suppliers, including 12 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of danthron were found. A report filed in 1986 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of danthron totaled 10,000 to 500,000 lb; no later reports were filed (EPA 2004).

Exposure

Historically, the primary route of potential human exposure to danthron has been oral administration of laxatives. Shortly before its withdrawal from the market, danthron was available from nine companies in over-the-counter products. The following products were voluntarily withdrawn from the market in the United States in 1987: Altan, Antrapurol, Bancon, Benno, DanSunate D, Danthron, Diaquone, Dionone, Dorban, Dorbane, Duolax, Fructines-Vichy, Istin, Istizin, Julax, Laxanorm, Laxans, Laxanthreen, Laxenta, Laxipur, Laxipurin, Modane, Neokutin S, Pastomin, Prugol, Roydan, Scatron D, Solven, Unilax, and Zwitsalax (NTP 1999). Danthron occurs naturally in several species of plants and insects. It has been isolated from dried leaves and stems of *Xyris semifuscata* harvested in Madagascar and forms the basic structure of the aglycones of naturally occurring laxative glycosides. Danthron has been identified in larvae of the elm-leaf beetle, *Pyrrhalta luteola;* it has been suggested that the insect biosynthesizes a mixture of anthraquinones and anthrones as protection from predators (IARC 1990).

Occupational exposure to danthron potentially could have occurred among health professionals during preparation and administration of the pharmaceutical and among workers involved in its formulation and packaging. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 357 workers (in the Health Services industry), including 187 women, potentially were exposed to danthron (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Products containing danthron as a laxative are no longer generally recognized as safe and effective and may not be marketed in the United States.

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Patel PM, Selby PJ, Deacon J, Chilvers C, McElwain TJ. 1989. Anthraquinone laxatives and human cancer: an association in one case. *Postgrad Med J* 65(762): 216-217.

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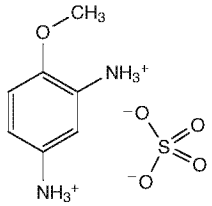
Sugie S, Mori Y, Okumura A, Yoshimi N, Okamoto K, Sato S, Tanaka T, Mori H. 1994. Promoting and synergistic effects of chrysazin on 1,2-dimethylhydrazine-induced carcinogenesis in male ICR/CD-1 mice. *Carcinogenesis* 15(6): 1175-1179.

2,4-Diaminoanisole Sulfate

CAS No. 39156-41-7

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

2,4-Diaminoanisole sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2,4-diaminoanisole sulfate caused thyroid-gland tumors in mice and rats, as well as tumors at several other tissue sites in rats. Dietary administration of 2,4-diaminoanisole sulfate caused thyroid-gland cancer (follicular-cell carcinoma or papillary adenocarcinoma or cystadenocarcinoma) in rats of both sexes and increased the combined incidence of benign and malignant C-cell tumors of the thyroid gland (adenoma and carcinoma) in male rats. In mice, it increased the combined incidence of benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma) in females and benign thyroid-gland tumors (follicular-cell adenoma) in males. Dietary administration of 2,4-diaminoanisole sulfate also caused cancer of the Zymbal gland (squamous-cell carcinoma or sebaceous adenocarcinoma) in rats of both sexes. In male rats, it also caused cancer of the skin (squamous- or basal-cell carcinoma or sebaceous adenocarcinoma) and increased the combined incidence of benign and malignant tumors of the preputial gland (adenoma, papilloma, and carcinoma). In female rats, it also caused cancer of the clitoral gland (squamous- or sebaceous-cell carcinoma) and the mammary gland (adenocarcinoma); these animals also developed tumors of the pituitary gland (IARC 1978, 1982, NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,4-diaminoanisole sulfate. Epidemiological studies have been conducted on professional and personal users of hair dyes; however, none of these studies specifically mentioned possible exposure to 2,4-diaminoanisole sulfate (IARC 2001).

Properties

2,4-Diaminoanisole sulfate is an aromatic amine salt that is an off-white to violet powder at room temperature (IARC 1978, 1982). It is soluble in water and ethanol and insoluble in sodium hydroxide. Physical and chemical properties of 2,4-diaminoanisole sulfate are listed in the following table.

Property	Information
Molecular weight	236.3[a]
Melting point	66°C to 67°C[b]
Boiling point	149°C to 150°C at 5 mm Hg[b]
Log K_{ow}	4.19[c]
Water solubility	1,000 g/L at 25°C[c]
Vapor pressure	1.05×10^{-14} mm Hg[c]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

2,4-Diaminoanisole sulfate has been used primarily as a component of oxidizing "permanent" hair- and fur-dye formulations. In 1978, about 75% of hair-dye formulations contained 2,4-diaminoanisole or its sulfate. However, a U.S. regulation requiring a warning label on all hair dyes containing 2,4-diaminoanisole or its sulfate was to become effective in April 1980, and the chemicals were voluntarily removed from products before that time (IARC 1982). 2,4-Diaminoanisole also has been used as an intermediate in the production of C.I. basic brown 2, which has been used to dye furs, acrylic fibers, cotton, wool, nylon, polyester, leather, and suede and has been an ingredient of shoe polishes (IARC 1978, 1982).

Production

Commercial production of 2,4-diaminoanisole sulfate in the United States was first reported in 1967, but no production has been reported since 1971 (IARC 1978). In 1977, annual usage of 2,4-diaminoanisole sulfate in the United States was estimated at 30,000 lb (NCI 1978). No data were found regarding U.S. production, imports, or exports of 2,4-diaminoanisole sulfate after its voluntary removal from hair dyes. In 2009, 2,4-diaminoanisole sulfate was produced by one manufacturer (in Europe) (SRI 2009) and was available from seven suppliers worldwide, including four U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of potential human exposure to 2,4-diaminoanisole sulfate are dermal contact and inhalation. Consumers who used hair dyes containing 2,4-diaminoanisole sulfate could have been exposed. In 1973, it was estimated that 40% of U.S. women were regular users of hair dyes. Most of the dyes used were of the permanent type, and certain of these products used 2,4-diaminoanisole sulfate as a color modifier. Before its removal from consumer products, the maximum concentration of 2,4-diaminoanisole sulfate in concentrated hair-dye preparations was approximately 1.5%. Therefore, substantial exposure of the general population to 2,4-diaminoanisole sulfate was possible (NCI 1978). No releases of 2,4-diaminoanisole sulfate to the environment were reported in the U.S. Environmental Protection Agency's Toxics Release Inventory from 1988 to 2007; however, small amounts of 2,4-diaminoanisole were released to air in 1989 (250 lb) and 1990 (26 lb) (TRI 2009). Occupational exposure could have occurred among workers at chemical- and dye-production facilities and workers using dyes containing 2,4-diaminoanisole sulfate to dye furs, textiles, and leather. Hairdressers and cosmetologists could have been exposed through the use of hair dyes containing 2,4-diaminoanisole sulfate (NCI 1978).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Food and Drug Administration (FDA)

Hair dyes containing 2,4-diaminoanisole sulfate must contain a warning statement that the product contains an ingredient that can penetrate skin and has been determined to cause cancer in laboratory animals.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) for 2,4-diaminoanisole and its salts = minimize occupational exposure (especially skin exposures).

2,4-Diaminoanisole and its salts are listed as a potential occupational carcinogens.

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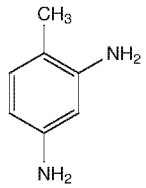
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select 2,4-Diaminoanisole sulfate.

2,4-Diaminotoluene

CAS No. 95-80-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

2,4-Diaminotoluene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

2,4-Diaminotoluene caused tumors in rats at several different tissue sites and by two different routes of exposure. Oral exposure to 2,4-diaminotoluene caused liver cancer (hepatocellular carcinoma) in male rats, and subcutaneous injection of 2,4-diaminotoluene caused cancer (sarcoma) at the injection site in rats of both sexes (IARC 1978).

Since 2,4-diaminotoluene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Dietary administration of 2,4-diaminotoluene caused liver cancer (hepatocellular carcinoma) in female mice and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats of both sexes. It also caused benign tumors of the subcutaneous tissue (fibroma) in male rats and increased the combined incidence of benign and malignant mammary-gland tumors (adenoma and carcinoma) in female rats. Lymphoma observed in female rats may also have been exposure-related (NCI 1979, IARC 1986). Administration of 2,4-diaminotoluene by stomach tube to male Eker rats (a strain with a high spontaneous incidence of kidney tumors) caused kidney cancer (carcinoma) (Morton *et al.* 2002).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,4-diaminotoluene.

Properties

2,4-Diaminotoluene is an aromatic amine that exists at room temperature as colorless-to-brown needle-shaped crystals. It is slightly soluble in water and very soluble in alcohol, ether, and benzene. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 2,4-diaminotoluene are listed in the following table.

Property	Information
Molecular weight	122.2[a]
Specific gravity	1.045 g/m^3 at 20°C[b]
Melting point	99°C[a]
Boiling point	292°C[a]
Log K_{ow}	0.337[a]
Water solubility	7.74 g/L at 25°C[c]
Vapor pressure	5.52×10^{-5} mm Hg[a]
Vapor density relative to air	4.2[b]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

The primary use of 2,4-diaminotoluene has been as an intermediate in the production of 2,4-toluene diisocyanate, which in turn is used to produce polyurethane (HSDB 2009). 2,4-Diaminotoluene has been used in the production of about 60 dyes, 28 of which are believed to have been produced in significant amounts in the mid 1970s. These dyes generally have been used to color silk, wool, paper, furs, and leather. Some have also been used to dye cotton fibers and other cellulosic fibers, in spirit varnishes and wood stains, as indicators in the manufacture of pigments, and as biological stains. 2,4-Diaminotoluene has been used as a developer for direct dyes, particularly to obtain black, dark blue, and brown shades, and to obtain navy blue and black colors on leather. It was also used in hair-dye formulations until this use ceased in the United States in 1971 (IARC 1978). Other applications include the preparation of impact resins, polyamides with superior wire-coating properties, antioxidants, hydraulic fluids, urethane foams, and fungicide stabilizers, and as a photographic developer (HSDB 2009).

Production

2,4-Diaminotoluene has been produced commercially in the United States since 1919. It is produced as a mixture of four diaminotoluene isomers (2,4-, 2,6-, 2,3-, and 3,4-diaminotoluene) by nitrating toluene to the dinitrotoluene isomers and reducing the mixture to the diaminotoluene isomers (IARC 1978). In 2009, 2,4-diaminotoluene was produced by nine manufacturers worldwide, including two in the United States (SRI 2009), and was available from 25 suppliers worldwide, including 18 U.S. suppliers (ChemSources 2009). U.S. imports and exports of 2,4-diaminotoluene are reported as part of a category of similar compounds, including *o*-, *m*-, and *p*-phenylenediamine, diaminotoluenes, and their derivatives and salts. Imports in this category ranged from 660,000 to 1.5 million pounds between 1989 and 2002, increasing to 4.7 million pounds in 2009. During this period, exports in this category grew from 42 million pounds in 1989 to a high of 161 million pounds in 2000 and 2003; 106.5 million pounds was exported in 2008 (USITC 2009). Reports filed in 1986, 1990, and

1994 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 2,4-diaminotoluene totaled 100 million to 500 million pounds; the reported quantities fell to between 10,000 and 500,000 lb in 1998 and 2002 (EPA 2004).

Exposure

The routes of potential human exposure to 2,4-diaminotoluene are dermal contact, ingestion, surgical implantation, and inhalation (Sepai *et al.* 1995, Luu *et al.* 1998, EPA 2005, HSDB 2009, TRI 2009). 2,4-Diaminotoluene has been identified as a hydrolytic degradation product of polyester urethane foam used to cover silicone breast implants (Luu *et al.* 1998). Levels as high as 6 ng/mL were detected in plasma and urine of patients one month after surgery, and measurable levels were detected in patients up to two years after surgery (Sepai *et al.* 1995, Luu *et al.* 1998). Small amounts of 2,4-diaminotoluene have also been reported to be released from boil-in bags upon prolonged boiling (HSDB 2009).

It was estimated that 16.5 million pounds of 2,4-diaminotoluene was released during production in 1977 (HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of 2,4-diaminotoluene in most years before 2003 ranged from 500 to 4,000 lb and were mainly to air. However, over 6,000 lb was released to an off-site nonhazardous-waste landfill in 1991 and 54,000 lb to an off-site underground injection well in 1998. Since 2003, most 2,4-diaminotoluene waste has been sent to off-site hazardous and nonhazardous waste landfills. In 2007, releases totaled 18,220 lb, of which 17,000 lb was released to an off-site hazardous-waste landfill and nearly all of the rest to air (TRI 2009). When 2,4-diaminotoluene is released to air, it may photolyze and react with photochemically generated hydroxyl radicals, with an estimated half-life of 8 hours. When it is released to water, it most likely will remain in solution, where it is subject to biodegradation and photooxidation. Because it is soluble in water and has a low soil sorption partition coefficient, it will most likely leach into the subsurface when released to soil. However, it is not likely to volatilize from either water or soil (HSDB 2009).

Because 2,4-diaminotoluene can be produced from the hydrolysis of toluene diisocyanate, an intermediate in the production of polyurethane, occupational exposure to 2,4-diaminotoluene can occur through inhalation of air in polyurethane manufacturing plants (IARC 1978, EPA 2005). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 8,511 workers (in the Textile Mill Products, Paper and Allied Products, Printing and Publishing, Chemicals and Allied Products, and Transportation Equipment industries), including 396 women, potentially were exposed to 2,4-diaminotoluene (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture or use of 2,4-diaminotoluene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Production is subject to discharge limitations.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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Luu HM, Hutter JC, Bushar HF. 1998. A physiologically based pharmacokinetic model for 2,4-toluenediamine leached from polyurethane foam-covered breast implants. *Environ Health Perspect* 106(7): 393-400.

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Sepai O, Henschler D, Czech S, Eckert P, Sabbioni G. 1995. Exposure to toluenediamines from polyurethane-covered breast implants. *Toxicol Lett* 77(1-3): 371-378.

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USITC. 2009. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 292151. Last accessed: 4/21/09.

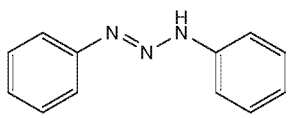
Diazoaminobenzene

CAS No. 136-35-6

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as 1,3-diphenyltriazene



Carcinogenicity

Diazoaminobenzene is *reasonably anticipated to be a human carcinogen* based on (1) evidence from studies in experimental animals and with human tissue demonstrating that diazoaminobenzene is metabolized to benzene, a known human carcinogen, and (2) evidence that diazoaminobenzene causes genetic damage. Studies in rats and mice have shown that the metabolism of diazoaminobenzene to benzene is quantitative. Benzene was listed in the First Annual Report on Carcinogens in 1980 based on human epidemiological studies dem-

onstrating that exposure to benzene causes leukemia. Benzene also causes cancer at numerous tissue sites in rodents.

Studies on Mechanisms of Carcinogenesis

Diazoaminobenzene is metabolized to benzene and to the known rodent carcinogen aniline; it also shares similar genotoxic and toxicological properties with these two carcinogens (Bordelon *et al.* 2005). In studies on the absorption, distribution, metabolism, and excretion of diazoaminobenzene orally administered to rats and mice, benzene and aniline were detected in blood, benzene was detected in exhaled breath, and metabolites of benzene and aniline were excreted in urine. Exhalation of benzene implies systemic exposure to this metabolite (Mathews and De Costa 1999; NTP 2002). Metabolites of diazoaminobenzene in the blood of rats and the urine of rats and mice included hydroquinone, muconic acid, and phenylmercapturic acid, which share benzene oxide as a common intermediate, demonstrating that the metabolic pathway of diazoaminobenzene is similar to that of benzene. In studies with human liver slices, diazoaminobenzene was reduced to benzene and aniline (Mathews and De Costa 1999). The proposed metabolic pathway for diazoaminobenzene is reductive cleavage by liver enzymes or by bacteria in the digestive tract to form benzene, aniline, and nitrogen. Benzene and aniline then are metabolized by cytochrome P450 and conjugating enzymes. Electron spin resonance studies have shown that in rats, phenyl radicals also are produced as intermediates in metabolism of diazoaminobenzene to benzene (Kadiiska *et al.* 2000).

In 16-day toxicity studies of rats and mice exposed to diazoaminobenzene (dermally, but without protection of the application site, to allow oral exposure through grooming), the symptoms observed were similar to those characteristic of benzene or aniline toxicity. Diazoaminobenzene also appeared to induce toxic effects not observed with aniline or benzene, including skin lesions at the application site (NTP 2002).

Diazoaminobenzene caused mutations in bacteria with mammalian microsomal metabolic activation (Zeiger *et al.* 1987). It also caused chromosomal aberrations in plants and micronucleus formation in the bone marrow of rodents (Ress *et al.* 2002). Benzene and aniline do not cause mutations in bacteria, but they do induce micronucleus formation in rodents. However, diazoaminobenzene orally administered to mice induced more micronuclei than did equimolar doses of benzene or a mixture of benzene and aniline. The greater genotoxicity of diazoaminobenzene than of its metabolites benzene and aniline may be due to the effects of phenyl radicals formed during its metabolism.

Cancer Studies in Experimental Animals

No studies were identified that evaluated whether exposure to diazoaminobenzene to caused cancer in experimental animals.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to diazoaminobenzene.

Properties

Diazoaminobenzene is an aromatic amine that exists as small golden-yellow crystals at room temperature. It is insoluble in water but freely soluble in benzene, ether, and hot alcohol. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of diazoaminobenzene are listed in the following table.

Property	Information
Molecular weight	197.1[a]
Melting point	98°C[a]
Boiling point	305°C[b]
Log K_{ow}	3.99[c]
Water solubility	0.500 g/L[c]
Vapor pressure	1.91×10^{-5} mm Hg at 25°C[c]
Vapor density relative to air	6.8[b]
Dissociation constant (pK_b)	13.00[b]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

Diazoaminobenzene is used as a chemical intermediate, complexing agent, and polymer additive (Mathews and De Costa 1999). It has uses associated with organic synthesis and dye and insecticide manufacture (Lewis 1997), and it is an effective dopant for laser ablation (micro-machining) of polymethylmethacrylate (Bolle *et al.* 1990). Diazoaminobenzene has been identified as a low-level contaminant in the dyes D&C red no. 33, FD&C yellow no. 5 (tartrazine), and FD&C yellow no. 6; all three are permitted for use in drugs and cosmetics, and the latter two are permitted in food (FDA 2010).

Production

Diazoaminobenzene is produced by reaction of aniline with isoamyl nitrate (Smith and Ho 1990) or by diazotization of aniline dissolved in hydrochloric acid with sodium nitrite, followed by addition of sodium acetate (HSDB 2009). No information was found on levels of diazoaminobenzene production in the United States. Diazoaminobenzene was available from five U.S. suppliers in 2009 (ChemSources 2009). U.S. imports of diazoaminobenzene and *p*-aminoazobenzenedisulfonic acid (combined category) totaled 34,877 lb in 2008 (USITC 2009).

Exposure

The general population may be exposed to diazoaminobenzene through ingestion of products containing dyes or colorants or dermal exposure to such products. A 1977 study by the National Academy of Sciences reported average daily intakes of 43 mg for yellow no. 5 and 37 mg for yellow no. 6 (Feingold 2002). Thus, theoretical maximum average daily exposures to diazoaminobenzene are approximately 1.7 ng for yellow no. 5 and 1.5 ng for yellow no. 6, based on its maximum allowable levels in colorants under U.S. Food and Drug Administration regulations. Occupational exposure to diazoaminobenzene could occur from its use as a chemical intermediate and polymer additive.

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA)

The maximum level of diazoaminobenzene in color additives is 40 ppb for FD&C yellow no. 5 and no. 6 and 125 ppb for D&C red no. 33.

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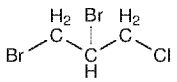
1,2-Dibromo-3-chloropropane

CAS No. 96-12-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as DBCP



Carcinogenicity

1,2-Dibromo-3-chloropropane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,2-dibromo-3-chloropropane caused tumors in two rodent species and at several different tissue sites. 1,2-Dibromo-3-chloropropane administered by stomach tube caused cancer of the forestomach (squamous-cell carcinoma) in rats and mice of both sexes and mammary-gland cancer (carcinoma) in female rats (NCI 1978).

Since 1,2-dibromo-3-chloropropane was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified. Inhalation exposure to 1,2-dibromo-3-chloropropane caused cancer of the nasal cavity (adenocarcinoma, carcinoma, and/or squamous-cell carcinoma) in rats and mice of both sexes. It also increased the combined incidence of benign and malignant tumors of the lung (alveolar/bronchiolar adenoma and carcinoma) in mice of both sexes and the pharynx (squamous-cell papilloma and carcinoma) in female rats, and it caused benign tumors of the tongue (squamous-cell papilloma) in rats of both sexes and the adrenal gland (cortical adenoma) in female rats (NTP 1982, IARC 1999). Exposure to 1,2-dibromo-3-chloropropane in the tank water of male and female fish (species not reported) caused cancer of the liver (hepatocellular carcinoma) and bile duct (cholangiocarcinoma) (IARC 1999).

Cancer Studies in Humans

At the time 1,2-dibromo-3-chloropropane was listed in the *Second Annual Report on Carcinogens,* no epidemiological studies had been identified that evaluated the relationship between human cancer and exposure specifically to 1,2-dibromo-3-chloropropane. Since then, relevant studies in humans have been identified. The International Agency for Research on Cancer reviewed four cohort studies of workers occupationally exposed to 1,2-dibromo-3-chloropropane and one population-based case-control study (IARC 1999). Two of the four cohort studies found an excess of lung cancer in exposed workers. The third cohort study found excesses of liver and biliary-tract cancer, and the fourth found an excess of cervical cancer. However, in some of the studies, workers were exposed to other compounds in addition to 1,2-dibromo-3-chloropropane. IARC concluded that there was inadequate evidence to evaluate the relationship between human cancer and exposure specifically to 1,2-dibromo-3-chloropropane.

Properties

1,2-Dibromo-3-chloropropane is a halogenated aliphatic hydrocarbon which at room temperature is a colorless-to-brown liquid with a pungent odor (IARC 1999). It is slightly soluble in water and miscible with most aliphatic and aromatic hydrocarbons, oils (unspecified), dichloropropane, methanol, ethanol, isopropyl alcohol, and acetone. It may burn, although it does not ignite readily and is generally considered stable (Akron 2009). Physical and chemical properties of 1,2-dibromo-3-chloropropane are listed in the following table.

Property	Information
Molecular weight	236.4
Specific gravity	2.08 at 20°C/20°C
Melting point	5°C
Boiling point	164°C at 300 mm Hg
Log K_{ow}	2.96
Water solubility	1.2 g/L at 20°C
Vapor pressure	0.58 mm Hg at 20°C
Vapor density relative to air	2.09 at 14°C

Source: HSDB 2009.

Use

1,2-Dibromo-3-chloropropane was previously registered by the U.S. Environmental Protection Agency as a soil fumigant to control nematodes for field crops, vegetables, fruits, nuts, greenhouse and nursery crops, and turf (IARC 1979, ATSDR 1992, HSDB 2009). In 1977, EPA suspended registrations for the uses of products containing the compound except for use with pineapples in Hawaii; this exception was revoked in 1985 (ATSDR 1992). Since then, 1,2-dibromo-3-chloropropane has been used in the United States only as an intermediate in organic synthesis, such as in the synthesis of the fire retardant tris(2,3-dibromopropyl)phosphate, and for research purposes (ATSDR 1992, HSDB 2009).

Production

1,2-Dibromo-3-chloropropane was first synthesized in 1833 and first produced commercially in the United States in 1955 (IARC 1979). In 1969, U.S. production was 3.9 million kilograms (8.6 million pounds). Estimates of annual production in 1974 and 1975 were 18 million to 20 million pounds (IARC 1999), and in 1977, two companies producing 1,2-dibromo-3-chloropropane were identified (ATSDR 1992). 1,2-Dibromo-3-chloropropane is no longer commercially manufactured in the United States and was not reported to be produced for sale by any manufacturing plant worldwide in 2009 (ATSDR 1992, SRI 2009). Nevertheless, 21 suppliers were identified worldwide in 2009,

including 13 U.S. suppliers (ChemSources 2009). No information on U.S. imports or exports of 1,2-dibromo-3-chloropropane was found.

Exposure

Potential routes of exposure to 1,2-dibromo-3-chloropropane include inhalation, dermal contact, and ingestion (NCI 1978). Widespread exposure of the general population or of workers to 1,2-dibromo-3-chloropropane is not likely, since registered uses of the chemical as a soil fumigant in the United States were cancelled in 1985 (ATSDR 1992). In 1974, U.S. farmers applied 9.8 million pounds of 1,2-dibromo-3-chloropropane; in 1977, 0.8 million pounds was used in California alone (HSDB 2009). Exposure of the general population to small quantities of 1,2-dibromo-3-chloropropane could still occur through ingestion or inhalation exposure to previously contaminated groundwater used as tap water and to food irrigated with contaminated groundwater. Household uses of groundwater, such as for bathing, showering, or dishwashing, might result in inhalation exposure (Clark and Snedeker 2005). However, exposure from contaminated groundwater is limited, because 1,2-dibromo-3-chloropropane was used in only a few geographical locations, and contamination is not widespread (IARC 1979, ATSDR 1992, Clark and Snedeker 2005). 1,2-Dibromo-3-chloropropane has been identified as a constituent of concern at eight hazardous-waste sites on EPA's National Priorities List, three each in California and Hawaii, and one each in Colorado and Florida (ATSDR 1992).

When released to air, 1,2-dibromo-3-chloropropane exists as a vapor and is degraded by photochemically produced hydroxyl radicals to 1,2-dibromopropanol, chlorobromopropanol, and 1-bromo-3-chloro-2-propanone, with a half-life of 37 days (HSDB 2009). Air concentrations measured while it was being applied in a vineyard by injection into the soil ranged from 3 ppb 5 feet above ground in the middle of the field to 11 ppb in the cab of the tractor pulling the injection rig. When released to surface water, 1,2-dibromo-3-chloropropane will volatilize rapidly. When released to soil, it may leach into groundwater or volatilize into the air, because it is not expected to bind strongly to soil or sediment (ATSDR 1992). Biodegradation in soil is possible, but is expected to be slow. Between 1978 and 1991, 1,2-dibromo-3-chloropropane was found in 1,829 of 20,545 groundwater-monitoring wells at concentrations of 0.001 to 8,000 µg/L. It was found in 275 drinking-water wells at concentrations of up to 7.4 µg/L.

The National Occupational Hazard Survey (conducted from 1972 and 1974) estimated that 9,682 workers were exposed to 1,2-dibromo-3-chloropropane (NIOSH 1976). No more recent estimates of the number of potentially exposed workers were found. However, its use as a soil fumigant was discontinued in 1985, and it is likely that only small amounts are used for chemical synthesis and research purposes. In 1977, exposure levels were estimated to range from less than 1 to 6 mg/m^3 (100 to 600 ppb) in production and formulation plants (IARC 1979).

Regulations

Department of Transportation (DOT)

1,2-Dibromo-3-chloropropane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations have been cancelled.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 1,2-dibromo-3-chloropropane = U066.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.0002 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.0002 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.001 ppm.

Comprehensive standards for occupational exposure to 1,2-dibromo-3-chloropropane have been developed.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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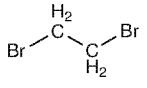
1,2-Dibromoethane

CAS No. 106-93-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as ethylene dibromide



Carcinogenicity

1,2-Dibromoethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,2-Dibromoethane caused tumors in rats and mice at several different tissue sites and by several different routes of exposure. Inhalation

exposure to 1,2-dibromoethane caused cancer of the nasal cavity (carcinoma and adenocarcinoma) and the blood vessels (hemangiosarcoma) in rats of both sexes and in female mice; benign or malignant lung tumors (alveolar/bronchiolar adenoma or carcinoma) in mice of both sexes and in female rats; and benign or malignant mammary-gland tumors (fibroadenoma or adenocarcinoma) in females of both species. It also caused testicular tumors (mesothelioma of the tunica vaginalis) in male rats and cancer of the subcutaneous tissue (fibrosarcoma) in female mice (NTP 1982). Dermal exposure to 1,2-dibromoethane caused lung and skin tumors in female mice (Van Duuren *et al.* 1979). Administration of technical-grade 1,2-dibromoethane by stomach tube caused cancer of the forestomach (squamous-cell carcinoma) in rats and mice of both sexes, blood-vessel cancer (hemangiosarcoma, primarily in the spleen) in male rats, benign lung tumors (alveolar-bronchiolar adenoma) in mice of both sexes, and liver cancer (hepatocellular carcinoma) in female rats (NCI 1978).

Since 1,2-dibromoethane was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified. Inhalation exposure to 1,2-dibromoethane caused blood-vessel cancer (hemangiosarcoma in the spleen) and increased the combined incidence of benign and malignant adrenal-gland tumors (cortical adenoma, carcinoma, and pheochromocytoma) in rats of both sexes. It also caused mammary-gland tumors in females and skin tumors (mesenchymal tumors) in males (Wong *et al.* 1982). In mice, administration of 1,2-dibromoethane in the drinking water caused forestomach tumors (squamous-cell carcinoma) in both sexes and benign tumors of the esophagus (papilloma) in females (Van Duuren *et al.* 1985). In fish, dietary administration of 1,2-dibromoethane caused benign glandular-stomach tumors (papilloma) in both sexes (Hendricks *et al.* 1995), and administration in the tank water caused benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma), bile duct (cholangioma and cholangiocarcinoma), and gall bladder (papillary adenoma and adenocarcinoma) (Hawkins *et al.* 1998).

Cancer Studies in Humans

At the time 1,2-dibromoethane was listed in the *Second Annual Report on Carcinogens,* the data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to 1,2-dibromoethane. Since then, additional epidemiological studies have been identified. Results from three studies of occupational exposure to 1,2-dibromoethane were inconclusive, because the workers were exposed to mixtures of chemicals, and the statistical power of the studies to detect an effect was low (IARC 1999).

Properties

1,2-Dibromoethane is a volatile saturated brominated hydrocarbon that exists at room temperature as a colorless liquid with a sweet, chloroform-like odor (Akron 2009). It is only slightly soluble in water but is miscible with many organic solvents, such as diethyl ether, ethanol, acetone, and benzene. 1,2-Dibromoethane is stable in closed containers under normal conditions (Akron 2009). Physical and chemical properties of 1,2-dibromoethane are listed in the following table.

Property	Information
Molecular weight	187.9[a]
Density	2.17 g/mL[a]
Melting point	10°C[a]
Boiling point	131°C to 132°C[a]
Log K_{ow}	1.96[a]
Water solubility	3.91 g/L at 25°C[b]
Vapor pressure	11.2 mm Hg at 25°C[a]
Vapor density relative to air	6.5[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Historically, the primary use of 1,2-dibromoethane has been as a lead scavenger in antiknock mixtures added to gasolines (IPCS 1996). Lead scavenging agents transform the combustion products of tetraalkyl lead additives to forms that are more likely to be vaporized from engine surfaces. In 1978, 90% of the 1,2-dibromoethane produced was used for this purpose (ATSDR 1992). Annual consumption of 1,2-dibromoethane in the United States has decreased since the U.S. Environmental Protection Agency banned the use of lead in gasoline.

Another major past use of 1,2-dibromoethane was as a pesticide and an ingredient of soil and grain fumigants and for post-harvest application to various vegetable, fruit, and grain crops (NTP 1982). It also was used to kill fruit flies on citrus fruits, mangoes, and papayas after harvest and in the soil to protect grasses in environments such as golf courses (ATSDR 1992). By 1984, EPA regulations had eliminated most of the uses of 1,2-dibromoethane as a pesticide in the United States. 1,2-Dibromoethane has been used as a chemical intermediate in the manufacture of resins, gums, waxes, dyes, and pharmaceuticals and as a high-density, nonflammable solvent in a number of applications. Small amounts of 1,2-dibromoethane have been used in the manufacture of vinyl bromide, which is used as a flame retardant (ATSDR 1992, HSDB 2009).

Production

Annual U.S. production of 1,2-dibromoethane peaked at 332 million pounds in 1974, but had declined to 170 million pounds by 1982 (ATSDR 1992, HSDB 2009). In 2009, 1,2-dibromoethane was produced by six manufacturers worldwide, including one in the United States, two in India, and one each in Europe, China, and the Middle East (SRI 2009), and was available from 36 suppliers worldwide, including 18 U.S. suppliers (ChemSources 2009). Imports in the category "ethylene dibromide and fluorinated, brominated, or iodinated derivatives of acyclic hydrocarbons" have varied considerably from 1989 to 2008, from zero in 2002, 2007, and 2008 to highs of over 2 million kilograms (4.4 million pounds) in 1997 and 2000 (USITC 2009). In 1978, U.S. exports of of 1,2-dibromoethane totaled 84.8 million pounds (ATSDR 1992), but from 1989 to 2008, exports declined from over 12 million kilograms (26 million pounds) to zero in 2007 and 2008 (USITC 2009). Reports filed under EPA's Toxic Substances Control Act Inventory Update Rule indicate that U.S. production plus imports of 1,2-dibromoethane declined from between 100 million and 500 million pounds in 1986 to between 1 million and 10 million pounds in 1998 and 2002 (EPA 2004).

Exposure

Potential routes of human exposure to 1,2-dibromoethane are inhalation of ambient air and ingestion of contaminated drinking water and foods. As a result of its historical use as a gasoline additive and a soil fumigant and its persistence in soil and groundwater, 1,2-dibromoethane has been detected in ambient air, soil, groundwater, and food (ATSDR 1992). According to EPA's Toxics Release Inventory, en-

vironmental releases of 1,2-dibromoethane have declined dramatically since 1988. Total releases were 99,000 lb in 1988, declining to 19,000 lb in 1994 and 10,000 lb in 2001. However, almost 48,000 lb was released in 1999. In 2007, 4,236 lb of 1,2-dibromoethane was released, over half of which was released by one facility to air (TRI 2009).

In 1980, concentrations of 1,2-dibromoethane in U.S. ambient air ranged from 0.12 to 2.826 ng/m^3. Daily intake through inhalation of ambient air was estimated to range from 0 to 79 µg/kg (IPCS 1996). In addition, inhalation of 1,2-dibromoethane released to indoor air from contaminated groundwater, such as while showering, may play an important role in human exposure. Concentrations in groundwater not used for drinking water were measured at up to 90 µg/L in an irrigation well in Georgia in the early 1980s. Because 1,2-dibromoethane is readily volatilized from water, measured concentrations in surface water have not exceeded 0.2 µg/L in the United States (ATSDR 1992).

An EPA study detected 1,2-dibromoethane in slightly over 1% of public water systems tested, at mean concentration of 3.6 µg/L (EPA 2001). In California, the mean concentration in active and closed public wells was 0.006 ppb (0.006 µg/L), well below the California Department of Health Services maximum contaminant level (MCL) of 0.02 ppb (0.02 µg/L) (Kloos 1996). However, 1,2-dibromoethane was present at concentrations above the MCL in groundwater at about half of the underground storage tank sites tested (Falta *et al.* 2005). In a rural county in Kansas, the municipal water supply exceeded the U.S. EPA MCL for 1,2-dibromoethane (0.05 µg/L) on six occasions, the highest reported concentration being 0.18 µg/L (Neuberger *et al.* 2004). EPA estimated daily intake of 1,2-dibromoethane from drinking water to range from 0 to 16 µg/kg (ATSDR 1992).

Groundwater and river water from areas with known 1,2-dibromoethane contamination have been used to flood cranberry bogs for irrigation. 1,2-Dibromoethane was found at concentrations of 0.04 to 0.15 µg/kg in cranberry fruits exposed to 1,2-dibromoethane-contaminated water; however, the authors concluded that most of the contamination seemed to be associated with the water on the crop and not with the flesh of the fruit (Xia and Rice 2001). In the U.S. Food and Drug Administration's Total Diet Study, 1,2-dibromoethane was found in 1 of 40 samples of sweet pickles at a concentration of 0.013 mg/kg (13 µg/kg) (FDA 2006). In Greece, where 1,2-dibromoethane has been used as a fumigant for the wax moth that attacks honey combs, it was found in 2 of 25 samples of honey from treated hives, at concentrations of 12 and 75 µg/kg (Tananaki *et al.* 2005). EPA estimated the maximum daily intake of 1,2-dibromoethane from food to be 0.09 µg/kg (ATSDR 1992).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 8,500 workers, including about 800 women, potentially were exposed to 1,2-dibromoethane (NIOSH 1990). Eight facilities requested that the National Institute for Occupational Safety and Health make health hazard evaluation studies of their workplaces to investigate potential exposure to 1,2-dibromoethane. 1,2-Dibromoethane was detected in the air at five workplaces (White and Lybarger 1977, Markel 1980, Okawa 1980, Arenholz 1983, Thorburn and Gunter 1983). At four workplaces, personal protective equipment was recommended, even though the air concentration in two workplaces was below the OSHA limit. In the fifth workplace, no toxic effects on workers were found, and no changes to work practices were recommended.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,2-dibromoethane on ships and barges.

Department of Transportation (DOT)

1,2-Dibromoethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of 1,2-dibromoethane is subject to certain provisions for the control of volatile organic compound emissions.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations with 1,2-dibromoethane as the active ingredient have been cancelled.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,2-dibromoethane = U067, K117, K118, K136.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.00005 mg/L.

Food and Drug Administration (FDA)

Action levels for 1,2-dibromoethane in food and animal feed range from 0.01 to 150 ppb.
Maximum permissible level in bottled water = 0.00005 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 20 ppm.
Ceiling concentration = 30 ppm.
Acceptable peak exposure = 50 ppm (maximum duration = 5 min).

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.045 ppm.
Ceiling recommended exposure limit = 0.13 ppm (15-min exposure).
Immediately dangerous to life and health (IDLH) limit = 100 ppm.
Listed as a potential occupational carcinogen.

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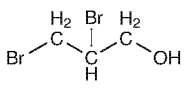
2,3-Dibromo-1-propanol

CAS No. 96-13-9

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as 2,3-dibromopropan-1-ol



Carcinogenicity

2,3-Dibromo-1-propanol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dermal exposure to 2,3-dibromo-1-propanol caused tumors at several different tissue sites in rats and mice. 2,3-Dibromo-1-propanol painted onto the skin increased the combined incidence of benign and malignant skin tumors (squamous-cell papilloma or carcinoma, basal-cell tumors, sebaceous adenoma, or keratoacanthoma) in rats and mice of both sexes. It also caused tumors (benign or malignant) at numerous other tissue sites, including the nasal mucosa, digestive tract, Zymbal gland, liver, and kidney in rats of both sexes; the mammary gland (adenocarcinoma) in female rats; the spleen (vascular tumors) and mesothelium (mesothelioma of the abdominal cavity or the tunica vaginalis of the testes) in male rats; the forestomach in mice of both sexes; and the liver and lung in male mice (NTP 1993, IARC 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,3-dibromo-1-propanol.

Studies on Mechanisms of Carcinogenesis

2,3-Dibromo-1-propanol was genotoxic in bacterial and mammalian *in vitro* test systems, including *Salmonella typhimurium, Escherichia coli,* V79 hamster cells, and L5178Y mouse lymphoma cells. It also caused sex-linked recessive lethal mutations and reciprocal translocations in *Drosophila melanogaster.* It caused sister chromatid exchange and chromosomal aberrations in cultured Chinese hamster ovary cells, but did not cause micronucleus formation in the bone marrow of mice administered 2,3-dibromo-1-propanol by intraperitoneal injection (IARC 2000). There is no evidence to suggest that mechanisms by which 2,3-dibromo-1-propanol causes tumors in experimental animals would not also operate in humans.

Properties

2,3-Dibromo-1-propanol is a halogenated alcohol that is a colorless to slightly yellow viscous liquid at room temperature. It is soluble in water, acetone, alcohol, ether, and benzene and is stable under normal temperatures and pressures (IARC 2000, Akron 2009). Physical and chemical properties of 2,3-dibromo-1-propanol are listed in the following table.

Property	Information
Molecular weight	217.9
Specific gravity	2.12 at 20°C/4°C
Melting point	8°C
Boiling point	219°C
Log K_{ow}	0.96
Water solubility	52 g/L at 25°C
Vapor pressure	0.09 mm Hg at 25°C
Vapor density relative to air	2.12

Source: HSDB 2009.

Use

The major use of 2,3-dibromo-1-propanol is as an intermediate in the production of flame retardants, insecticides, and pharmaceuticals, and the chemical itself has been used as a flame retardant. 2,3-Dibromo-1-propanol was used in the production of tris(2,3-

dibromopropyl) phosphate, a flame retardant used in children's clothing and other products (HSDB 2009). Tris(2,3-dibromopropyl) phosphate was banned from use in sleepwear in 1977 by the Consumer Product Safety Commission after studies showed that it caused cancer in experimental animals (NTP 1993, HSDB 2009).

Production

Production of 2,3-dibromo-1-propanol in the United States was more than 10 million pounds in 1976, but decreased drastically after the use of tris(2,3-dibromopropyl) phosphate in sleepwear was banned (NTP 1993). In 2009, 2,3-dibromo-1-propanol was produced by two manufacturers in East Asia (SRI 2009) and was available from 16 suppliers, including 9 U.S. suppliers (ChemSources 2009). Reports filed in 1986, 1990, and 1998 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 2,3-dibromo-1-propanol totaled 10,000 to 500,000 lb; no inventory update reports for 2,3-dibromo-1-propanol were filed in 1994 or 2002 (EPA 2004).

Exposure

The primary routes of human exposure to 2,3-dibromo-1-propanol are inhalation and dermal contact. 2,3-Dibromo-1-propanol is a metabolite of tris(2,3-dibromopropyl) phosphate in humans (NTP 1993). Over 50 million children who wore treated sleepwear before the 1977 ban may have been exposed to 2,3-dibromo-1-propanol as a metabolite of tris(2,3-dibromopropyl) phosphate (Blum *et al.* 1978). 2,3-Dibromo-1-propanol could be released into the environment through its production and use (HSDB 2009). If released to air, 2,3-dibromo-1-propanol is expected to exist as a vapor and to be degraded by photochemically produced hydroxide radicals, with a half-life of 8 days. It is not expected to volatilize from water or soil or to adsorb to soil or sediment, and so is expected to enter groundwater if released to water or soil. Limited data suggest that it might biodegrade under aerobic conditions and that the potential for bioaccumulation is low.

Occupational exposure to 2,3-dibromo-1-propanol could occur through inhalation and dermal contact in industries where 2,3-dibromo-1-propanol is produced or is used to produce flame-retardant materials, pharmaceuticals, and insecticides (HSDB 2009). No estimates of occupational exposure to 2,3-dibromo-1-propanol were found.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 2,3-dibromo-1-propanol were identified.

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1,4-Dichlorobenzene

CAS No. 106-46-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as *p*-dichlorobenzene

Carcinogenicity

1,4-Dichlorobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,4-dichlorobenzene caused tumors at several different tissue sites in mice and rats. Administration of 1,4-dichlorobenzene by stomach tube caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice of both sexes and kidney cancer (tubular-cell adenocarcinoma) and mononuclear-cell leukemia in male rats. It also increased the combined incidence of benign and malignant adrenal-gland tumors (pheochromocytoma) in male mice (IARC 1987, NTP 1987).

Since 1,4-dichlorobenzene was listed in the *Fifth Annual Report on Carcinogens,* an additional study in mice has been identified. Inhalation exposure to 1,4-dichlorobenzene caused liver cancer (hepatocellular carcinoma and hepatoblastoma or histiocytic sarcoma) in mice of both sexes (Aiso *et al.* 2005).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,4-dichlorobenzene. One cohort study reported five cases of leukemia associated with exposure to dichlorobenzenes (IARC 1974, 1982). The International Agency for Research on Cancer reviewed the evidence for the carcinogenicity of dichlorobenzenes in 1999, but reported no additional studies of human exposure to 1,4-dichlorobenzene (IARC 1999).

Properties

1,4-Dichlorobenzene is a chlorinated aromatic compound with a distinctive aromatic odor that is very strong at high concentrations. It is a white or colorless crystal at room temperature (Akron 2009, HSDB 2009). 1,4-Dichlorobenzene is practically insoluble in water; soluble in chloroform, carbon disulfide, benzene, and ether; and very soluble in ethanol and acetone. 1,4-Dichlorobenzene is noncorrosive, volatile, and combustible, and it is flammable when exposed to heat, flame, or oxidizers. When it is heated to decomposition, toxic gases and vapors (such as hydrochloric acid and carbon monoxide) are released (HSDB 2009). It is stable at room temperature under normal handling and storage in closed containers (Akron 2009). Physical and chemical properties of 1,4-dichlorobenzene are listed in the following table.

Property	Information
Molecular weight	147.0
Density	1.2475 g/mL at 20°C/4°C
Melting point	52.7°C
Boiling point	174°C at 760 mm Hg
Log K_{ow}	3.44
Water solubility	0.076 g/L at 25°C
Vapor pressure	1.7 mm Hg at 25°C
Vapor density relative to air	5.08

Source: HSDB 2009.

Use

1,4-Dichlorobenzene has been used primarily as a space deodorant in products such as room deodorizers and toilet deodorant blocks and as a fumigant for moth control (accounting for about 35% to 55% of the 1,4-dichlorobenzene produced) (ATSDR 1998). In 2007, it was used primarily as an intermediate in the production of polyphenylene sulfide, a plastic used in the electrical and electronics industries (52%), in the production of 1,2,4-trichlorobenzene room deodorant (22%), and for moth control (15%) (CMR 2004). Other uses of 1,4-dichlorobenzene include use as a germicide or disinfectant; a soil fumigant; an insecticide for fruit borers and ants; a chemical intermediate in the production of various dyes, pharmaceuticals, and resin-bonded abrasives; an agent to control mold and mildew growth on tobacco seeds, leather, and some fabrics; and an extreme-pressure lubricant (HSDB 2009).

Production

1,4-Dichlorobenzene was first produced commercially in the United States in 1915 (IARC 1982). In 2005, U.S. production capacity for 1,4-dichlorobenzene was reported to be 79 million pounds (CMR 2004). Demand is expected to grow by about 5% in the future because of growth in the production of polyphenylene sulfide resin, an engineering plastic that is used mainly for its insulating and dielectric properties. In 2009, 1,4-dichlorobenzene was produced by 32 manufacturers worldwide, including 1 each in the United States and Canada, 2 each in Mexico and East Asia, 4 in Europe, 9 in India, and 13 in China (SRI 2009), and it was available from 63 suppliers, including 22 U.S. suppliers (ChemSources 2009). U.S. imports of 1,4-dichlorobenzene reached a low of slightly less than 900,000 kg (2 million pounds) in 1990, increasing to almost 22 million kilograms (50 million pounds) in 2007. U.S. exports of 1,4-dichlorobenzene declined from a high of over 12 million kilograms (27 million pounds) in 2000 to slightly more than 0.5 million kilograms (1.2 million pounds) in 2005 (USITC 2009). According to reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule, U.S. production plus imports of 1,4-dichlorobenzene totaled 10 million to 50 million pounds in 1986 and 50 million to 100 million pounds between 1990 and 2002, decreasing to 10 million to 50 million pounds in 2006 (EPA 2004, 2009).

Exposure

The primary route of human exposure to 1,4-dichlorobenzene is inhalation; other potential routes are ingestion and dermal contact (ATSDR 2006). The major potential sources of consumer exposure are its uses as a deodorizer and a moth-control agent. For this reason, indoor air concentrations exceed outdoor concentrations by at least an order of magnitude. Concentrations of 1,4-dichlorobenzene in urban areas and in the vicinity of hazardous waste sites generally average less than 25.2 μg/m^3, but indoor air concentrations may be one to three orders of magnitude higher where it is used as a space deodorizer or moth repellent. 1,4-Dichlorobenzene has been detected in meat and eggs from exposed animals and in fish from contaminated waters (IARC 1982). In the U.S. Food and Drug Administration's Total Diet Study, the concentrations measured in food and water were generally low, and exposure was less than that from air (ATSDR 2006). 1,4-Dichlorobenzene was detected 102 times in 33 different food items, at concentrations ranging from 0.002 to 0.29 ppm (in popcorn popped in oil) (FDA 2006). It has also been identified in samples of pig back fat at a concentration of 502 ng/g (Rius *et al.* 2005). Concentrations of 1,4-dichlorobenzene measured in fresh vegetables in the United Kingdom ranged from 0.027 μg/kg of fresh weight in potatoes to 0.464 μg/kg in peas (Wang and Jones 1994).

In 1988, EPA's Toxics Release Inventory reported environmental releases of 1.9 million pounds of 1,4-dichlorobenzene, mostly (> 99%) to air. Releases have since declined steadily; in 2007, 11 facilities released a total of 79,317 lb, mostly to air (TRI 2009). When released to water, 1,4-dichlorobenzene volatilizes rapidly; concentrations measured in surface water are generally low (median concentration < 1 ppb) (ATSDR 2006). However, concentrations as high as 400 ppb were measured in 2006 in canal water in a rural settlement in Matamoros, Tamaulipos, Mexico, along the U.S. border (Owens and Niemeyer 2006). 1,4-Dichlorobenzene was also measured in sediments from Bayou d'Inde, a tributary of the Calcasieu River near Lake Charles, Louisiana, at a concentration of 9.5 mg/kg in the solid portion and 67.1 μg/L in the interstitial water (Prytula and Pavlostathis 1996). Measured concentrations for river environments in Canada were 0.6 to 130 ng/L in water, 520 to 34,000 ng/g of dry weight in sediment, and 920 ng/m^3 in the atmosphere (Warren *et al.* 2007). In sampling of groundwater in the Edwards Aquifer, in Texas, only 3 of 27 wells had concentrations above the detection limit of 4 ng/L (Buszka *et al.* 1995). 1,4-Dichlorobenzene was also identified in municipal solid waste in Huntsville, Alabama, at a concentration of 5.8 μg/kg (Leahy *et al.* 2004).

Occupational exposure to 1,4-dichlorobenzene occurs during its manufacture, its conversion to polyphenylene sulfide, and its other industrial uses. Concentrations of up to 4,350 mg/m^3 have been measured in the air for various factory operations. In 1980, EPA reported that about 1 million workers in the United States were exposed to 1,4-dichlorobenzene, primarily by inhalation, whereas an industry survey from the same year reported that fewer than 1,000 workers were exposed during production, captive use, and shipment of 1,4-dichlorobenzene from producers (NTP 1987). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 33,978 workers, including 9,412 women, potentially were exposed to 1,4-dichlorobenzene (NIOSH 1990).

Regulations

Department of Transportation (DOT)

1,4-Dichlorobenzene is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of 1,4-dichlorobenzene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 63 μg/L; based on fish or shellfish consumption only = 190 μg/L.
Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 7.5 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,4-dichlorobenzene = U072, K149, K150.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.075 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.075 mg/L.
Polyphenylene sulfide resins produced by the reaction of 1,4-dichlorobenzene and sodium sulfide may be used in coatings that come in contact with food, provided the maximum residual 1,4-dichlorobenzene levels do not exceed 0.8 ppm and other requirements are met.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 75 ppm (450 mg/m^3).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 150 ppm.
Listed as a potential occupational carcinogen.

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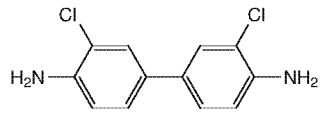
3,3′-Dichlorobenzidine and Its Dihydrochloride

CAS Nos. 91-94-1 and 612-83-9

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

3,3′-Dichlorobenzidine and 3,3′-dichlorobenzidine dihydrochloride are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The names 3,3′-dichlorobenzidine and 3,3′-dichlorobenzidine dihydrochloride are used interchangeably in the published literature. Although only the dihydrochloride salt is believed to be available commercially, it is not always clear whether the salt or the free base was the compound studied.

Cancer Studies in Experimental Animals

3,3′-Dichlorobenzidine or its dihydrochloride caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Dietary administration of 3,3′-dichlorobenzidine caused mammary-gland cancer (adenocarcinoma) in rats of both sexes, granulocytic leukemia and Zymbal-gland cancer (carcinoma) in male rats, urinary-bladder cancer (transitional-cell or papillary transitional-cell carcinoma) in hamsters and in female dogs, and liver cancer (hepatocellular carcinoma) in female dogs (IARC 1974, Stula *et al.* 1975, 1978). Subcutaneous injection of 3,3′-dichlorobenzidine caused skin and mammary-gland tumors in rats (IARC 1974). Since 3,3′-dichlorobenzidine was listed in the *Second Annual Report on Carcinogens*, additional studies in mice have been identified. Prenatal exposure to 3,3′-dichlorobenzidine caused lymphoid leukemia (IARC 1982), and dietary exposure caused liver cancer (hepatocellular carcinoma) in males (IARC 1982, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically

to 3,3′-dichlorobenzidine or 3,3′-dichlorobenzidine dihydrochloride. In three retrospective epidemiological studies, no urinary-bladder tumors were reported in men occupationally exposed to 3,3′-dichlorobenzidine (Gerarde and Gerarde 1974, Gadian 1975, MacIntyre 1975). These studies were limited by low statistical power and short follow-up time (less than 15 years for most workers).

Since 3,3′-dichlorobenzidine was listed in the *Second Annual Report on Carcinogens,* additional epidemiological studies have been identified. Three cohort studies reported an excess of bladder cancer among paperboard-printing workers (Sinks *et al.* 1992), chemical-manufacturing workers (Ouellet-Hellstrom and Rench 1996), and dye-manufacturing workers (Rosenman and Reilly 2004) who were potentially exposed to 3,3′-dichlorobenzidine; however, the workers potentially were also exposed to other substances associated with urinary-bladder cancer, such as *o*-toluidine or benzidine. One of the cohort studies (Ouellet-Hellstrom and Rench 1996) found a significant increase in the standardized incidence ratio for urinary-bladder cancer among chemical manufacturing plant workers potentially exposed to 3,3′-dichlorobenzidine who were first employed after benzidine manufacture had ended. Although pigments containing 3,3′-dichlorobenzidine were reported to have been used at the plant employing the paperboard-printing workers, exposure to 3,3′-dichlorobenzidine could not be verified by environmental measurements; this study also found an increased risk of kidney-cancer incidence and mortality (Sinks *et al.* 1992). A significant increase in cancer of the blood cells (mostly leukemia) was found among dye-manufacturing workers exposed only to 3,3′-dichlorobenzidine (Rosenman and Reilly 2004).

Properties

3,3′-Dichlorobenzidine is a chlorinated aromatic amine derived from benzidine (IARC 1974). It exists at room temperature as gray to purple needle-like crystals. It is slightly soluble in water and dilute hydrochloric acid, but readily soluble in benzene, diethyl ether, ethanol, and glacial acetic acid. Physical and chemical properties of 3,3′-dichlorobenzidine are listed in the following table.

Property	Information
Molecular weight	253.1[a]
Melting point	132°C to 133°C[a]
Boiling point	402°C[a]
Log K_{ow}	3.51[a]
Water solubility	0.0031 g/L at 25°C[a]
Vapor pressure	2.56×10^{-7} mm Hg at 25°C[b]
Dissociation constant (pK_a)	3.2[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

3,3′-Dichlorobenzidine is used in the United States primarily in the manufacture of pigments for printing ink, textiles, paper, paint, rubber, and plastics and as a curing agent for isocyanate-containing polymers and solid urethane plastics (IARC 1974, ATSDR 1998). As of 1983, at least seven synthetic organic pigments, toners, and lakes were produced with 3,3′-dichlorobenzidine. The yellow pigments derived from the chemical and its salts, including benzidine yellow, can be used as substitutes for the lead chromate pigments (ATSDR 1998, HSDB 2009). Use of 3,3′-dichlorobenzidine to synthesize dyes ceased in 1986 with the introduction of better dyes from other sources; however, its use in the manufacture of pigments has continued (ATSDR 1998). Both 3,3′-dichlorobenzidine and its dihydrochloride also are used in a color test for the detection of gold (IARC 1982). In addition, 3,3′-dichlorobenzidine is used in the production of tetraaminobiphenyl, which is used to produce polybenzimidazole, a thermally stable polymer used in protective clothing such as firefighters' apparel and high-temperature gloves. 3,3′-Dichlorobenzidine has also been used as a compounding ingredient for rubber and plastics (ATSDR 1998).

Production

Commercial production of 3,3′-dichlorobenzidine in the United States began in 1938 (IARC 1974). Production volumes of 3,3′-dichlorobenzidine were considered confidential by individual companies and therefore were not available (ATSDR 1998). In 2009, 3,3′-dichlorobenzidine was produced by one manufacturer, in Europe, and the hydrochloride was produced by 10 manufacturers, including 1 each in Europe and China, 2 in East Asia, and 6 in India (SRI 2009). 3,3′-Dichlorobenzidine was available from 14 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2009). The dihydrochloride is imported; imports peaked in 2000 at 8.7 million pounds, falling to 5.4 million pounds by 2008 (USITC 2009). The quantity of pigments derived from 3,3′-dichlorobenzidine totaled 129,000 lb in 1983 (ATSDR 1998). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 3,3′-dichlorobenzidine dihydrochloride totaled 1 million to 10 million pounds in 1986 and 1990 and 10 million to 50 million pounds between 1994 and 2006 (EPA 2004, 2009).

Exposure

The routes of potential human exposure to 3,3′-dichlorobenzidine are inhalation of airborne dust, ingestion of contaminated well water by those living near hazardous waste sites, and dermal contact, primarily during industrial operations. For the general population, the likelihood of exposure to 3,3′-dichlorobenzidine probably is low. Exposure via air, soil, or water is expected to be negligible, and the greatest likelihood of exposure to 3,3′-dichlorobenzidine is from improper land disposal. No current uses of 3,3′-dichlorobenzidine in commonly used consumer products were identified. In the past, exposure might have occurred during the use of pressurized spray containers of paints, lacquers, and enamels containing traces of benzidine yellow, a pigment derived from 3,3′-dichlorobenzidine (ATSDR 1998).

3,3′-Dichlorobenzidine may be released as atmospheric emissions or in wastewater during production or use as a dye intermediate. Atmospheric emissions most likely have been reduced by the adoption of closed-system operations. According to EPA's Toxics Release Inventory, environmental releases of 3,3′-dichlorobenzidine totaled 32 lb in 1999 (on-site releases), 1,000 lb in 2007, and 1,565 lb in 2008 (to off-site landfills) (TRI 2009). If released to air, 3,3′-dichlorobenzidine is expected to adsorb to particulate matter and photodegrade. If released to water, the free base will rapidly adsorb to sediment and particulate matter, where it will be bound. 3,3′-Dichlorobenzidine may undergo photolysis in water exposed to sunlight. If released to soil, it will bind to soil and possibly react with soil components. 3,3′-Dichlorobenzidine's strong tendency to partition to soils and sediments reduces the potential for human exposure (ATSDR 1998).

EPA reported in 1980 that data on the presence of 3,3′-dichlorobenzidine in the environment were limited; one survey detected 3,3′-dichlorobenzidine at concentrations of 0.13 to 3.0 mg/L at one 3,3′-dichlorobenzidine production waste-disposal site (IARC 1982). Between 1993 and 2003, 36 samples of surface water and sediment were taken from Lake Macatawa, in Holland, Michigan (Harden *et al.* 2005). Early samples contained 3,3′-dichlorobenzidine at concentrations exceeding the water-quality criteria by factors of up to 1,300; however, 3,3′-dichlorobenzidine was not detected in samples taken in 2003. Maximum concentrations of 3,3′-dichlorobenzidine in wastewater were estimated to be 10 ppb from metal finishing, 2 ppb (av-

erage = 0.3 ppb) from nonferrous metals manufacture, 10 ppb from paint and ink manufacture, and 3 ppb from coal mining (HSDB 2009).

Occupational exposure to the dihydrochloride probably continues to occur during its manufacture and conversion to derived pigments (HSDB 2009). No data were found on the number of workers potentially exposed to 3,3′-dichlorobenzidine dihydrochloride.

Regulations

Department of Transportation (DOT)

3,3′-Dichlorobenzidine is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 3,3′-Dichlorobenzidine is listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: 3,3′-Dichlorobenzidine is listed as a toxic pollutant.

Water Quality Criteria: For 3,3′-dichlorobenzidine, based on fish or shellfish and water consumption = 0.021 µg/L; based on fish or shellfish consumption only = 0.028 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for 3,3′-dichlorobenzidine.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 3,3′-dichlorobenzidine = U073.

3,3′-Dichlorobenzidine is listed as a hazardous constituent of waste.

Mine Safety and Health Administration

To control airborne exposure, 3,3′-dichlorobenzidine shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

3,3′-Dichlorobenzidine is listed as a potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure to 3,3′-dichlorobenzidine by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

3,3′-Dichlorobenzidine and its salts are listed as potential occupational carcinogens.

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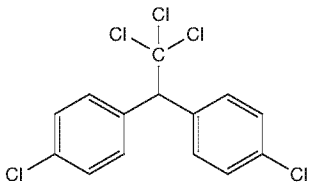
Dichlorodiphenyltrichloroethane

CAS No. 50-29-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as DDT or 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane



Carcinogenicity

Dichlorodiphenyltrichloroethane (DDT) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

DDT caused liver tumors in two rodent species and by two different routes of exposure. It caused primarily malignant primary liver-cell tumors (hepatocellular carcinoma) in mice of both sexes and in rats (of unspecified sex) following dietary exposure; in mice of both sexes following administration by stomach tube; and in female mice following subcutaneous injection (reviewed by IARC 1991). Increased incidences of lung tumors and malignant lymphoma following oral exposure to DDT were observed in some, but not all, of the studies in mice.

Cancer Studies in Humans

No epidemiological studies of the carcinogenicity of DDT in humans were identified at the time DDT was listed in the *Fourth Annual Report on Carcinogens.* Since then, a number of epidemiological studies of human cancer and DDT exposure have been identified. Studies

reviewed in 1991 by the International Agency for Research on Cancer were inconclusive because of coexposure to numerous pesticides and the small sizes of the study groups (IARC 1991).

Epidemiological studies conducted since 1991 have mainly been case-control or nested case-control studies, plus a few prospective or occupational cohort studies, and include over 20 studies of breast cancer. Comparison of the results of breast-cancer studies has been complicated by differences in exposure assessment, dietary factors, breast-tumor type and estrogen-receptor status, age, menopausal status, lactation history, body mass status, race or ethnicity, or exposure to other potential carcinogens (Snedeker 2001, Calle *et al.* 2002, Clapp *et al.* 2008, Eskenazi *et al.* 2009). The majority of breast-cancer studies (mostly of older women in the United States) did not find statistically significant associations with estimated exposure or with serum or adipose-tissue levels of DDT or 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (DDE, a metabolite of DDT) (see reviews above and ATSDR 2002, 2008, Lopez-Cervantes *et al.* 2004). However, positive associations between DDT exposure and breast cancer were reported in a few studies among women with higher levels of exposure and among certain subgroups of women (Wolff *et al.* 1993, Hoyer *et al.* 2000, Romieu *et al.* 2000, Rubin *et al.* 2006, Cohn *et al.* 2007).

Several studies have investigated the association between DDT or DDE exposure and cancer at other tissue sites. One study reported an association between DDT exposure and leukemia among agricultural workers (Morris-Brown *et al.* 1990). Increased risk or incidence of multiple myeloma with DDT exposure was found in a case-control study of farmers (Eriksson and Karlsson 1992) and a cohort proportionate-mortality study of pesticide applicators who had used 94% DDT (Cocco *et al.* 1997). Increased risk of liver cancer also has been associated with serum DDT level (McGlynn *et al.* 2006), DDT pesticide application (Cocco *et al.* 1997), and levels of DDE in adipose tissue (Cocco *et al.* 2000). Increased risks of cancer at other tissue sites, such as the gallbladder (Shukla *et al.* 2001), prostate (Settimi *et al.* 2003), and testes (McGlynn *et al.* 2008), have been reported in one study for each site.

Properties

DDT is a chlorinated aromatic hydrocarbon insecticide (NCI 1978) that in its pure form exists at room temperature as colorless to off-white needles or powder with a slight aromatic odor (Akron 2009, HSDB 2009). It is practically insoluble in water, but it is soluble in many organic solvents, including acetone, benzene, benzyl benzoate, carbon tetrachloride, chlorobenzene, cyclohexanone, ethanol, ethyl ether, gasoline, isopropanol, kerosene, morpholine, peanut oil, pine oil, tetralin, and tributyl phosphate (IARC 1974, HSDB 2009). DDT is highly soluble in lipids (HSDB 2009). It is very stable and exceptionally persistent in the environment (IPCS 1989). Technical-grade DDT is a mixture of three forms, *p,p′*-DDT (85%), *o,p′*-DDT (15%), and *o,o′*-DDT (trace amounts) (ATSDR 2002). Technical-grade DDT may also contain DDE and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD) as contaminants; both are breakdown products of DDT. Physical and chemical properties of DDT are listed in the following table.

Property	Information
Molecular weight	354.5
Specific gravity	0.98 to 0.99
Melting point	108.5°C
Boiling point	260°C
Log K_{ow}	6.91
Water solubility	5.50×10^{-6} g/L at 25°C
Vapor pressure	1.6×10^{-7} mm Hg at 20°C

Source: HSDB 2009.

Use

DDT was first used in the United States as an insecticide in 1939 (ATSDR 2002). From 1946 to 1972, DDT was one of the most widely used insecticides in the world (HSDB 2009). It was used for the control of insect pests such as the pink bollworm on cotton, codling moth on deciduous fruits, Colorado potato beetle, and European corn borer (ATSDR 2002). In the public health field, DDT was used to control malaria, typhus, and other insect-transmitted diseases and to treat body lice (HSDB 2009). It was also used for mothproofing clothing (ATSDR 2002). Its usage peaked in the 1960s, but in 1972, it was banned for the vast majority of uses in the United States (ATSDR 2002, HSDB 2009). DDT is currently used in the United States only under Public Health Service supervision for public health emergencies and by the U.S. Department of Agriculture or U.S. military for health quarantine. It is also still used in many countries where malaria is endemic, as an insecticide to control mosquitoes (HSDB 2009).

Production

Technical DDT was first synthesized in 1874, and commercial production in the United States had begun by 1945 (ATSDR 2002, HSDB 2009). In 1962, 82 million kilograms (180.4 million pounds) of DDT was produced in the United States for use on 334 agricultural commodities. In 1971, production in the United States was estimated at 2 million kilograms (4.4 million pounds) (ATSDR 2002). In 2009, no U.S. companies manufactured DDT, but it was produced by six companies worldwide, including one in Europe, two in China, one in East Asia, and two in India (SRI 2009), and was available from 21 suppliers, including 9 U.S. suppliers (Chem Sources 2009). DDT is no longer imported into the United States (ATSDR 2002); it was last imported in 1972, in the amount of about 200 metric tons (441,000 lb) (HSDB 2009). In 1978 (the last year for which export data specific to DDT were available), U.S. exports of DDT were 13.7 million kilograms (30.2 million pounds).

Exposure

Despite the 1972 U.S. ban of DDT, human exposure continues because of its extensive former use, its current use in some areas of the world, and the persistence of DDT and its breakdown products in the environment (ATSDR 2002). DDT is still released into the atmosphere through spraying in some areas of the world. In addition, it volatilizes from soil in areas where it was formerly used. The volatilization and deposition cycle may be repeated many times, resulting in widespread distribution of DDT worldwide. In addition, DDT readily accumulates in animal fat and thus bioaccumulates through the food chain. DDT and its breakdown products have been found throughout the world, from the Arctic to the Antarctic, having been detected in ambient and indoor air, precipitation (rain and snow), water, soil, and animal and plant tissues. The residual levels of DDT in the environment have declined and continue to decline, but because of DDT's high persistence, it will be present at low levels for decades. In a study of long-term dietary intake of DDT and all of its metabolites, daily intake for a 70-kg 16-year-old U.S. male was estimated at 6.5 µg for 1978–79, 2.4 µg for 1979–80, 1.5 µg for 1984–86, and 0.97 µg for 1986–91. Currently, human exposure to DDT and its breakdown products is primarily through dietary ingestion, particularly of meat, fish, poultry, and root and leafy vegetables. The highest dietary exposure occurs among indigenous Arctic populations that eat traditional foods such as seal, whale, or caribou. The highest average daily intake was observed in the eastern Arctic, where total daily intake of DDT and all of its metabolites was 24.2 to 27.8 µg/day. The foods contributing the most were beluga whale blubber (316 µg/g of wet weight) and narwhal whale blubber (273 µg/g) (ATSDR 2002).

DDT has been measured in numerous human tissues in the U.S. population and in other populations around the world, including indigenous Arctic peoples. DDT accumulates in fatty tissues and is usually found in higher concentrations in human milk than in cow's milk or other infant foods. In the United States, mean concentrations of DDT were 0.99 mg/kg (990 ng/g) in milk fat from Arkansas women in 1986, 28.8 ppb (ng/g) in serum from consumers of Great Lakes fish in 1982, and 252 ng/g in adipose tissue from a national sample of individuals age 45 years or older in 1986 (ATSDR 2002). The median concentration of DDT in plasma samples from 407 highly exposed Inuit individuals living in Greenland was 35 µg/kg of lipid (35 ng/g) (Bjerregaard *et al.* 2001). DDT was detected in 95% of the samples from this population. For the population measured in the United States National Health and Nutrition Examination Survey (NHANES), the geometric mean concentration of DDE in serum was 260 ng/g of lipid in 1999–2000, 285 ng/g in 2001–02 , and 238 ng/g in 2003–04 (ATSDR 2008). The Mexican-American population sampled in NHANES had mean DDE concentrations about twice those for the total population: 674 ng/g in 1999–2000, 652 ng/g in 2001–02, and 444 ng/g in 2003–04.

Regulations

Department of Transportation (DOT)

DDT is considered a hazardous substance and a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material, including transporting it in tank cars.

Environmental Protection Agency (EPA)

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00022 µg/L; based on fish or shellfish consumption only = 0.00022 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Federal Insecticide, Fungicide, and Rodenticide Act

Registrations for nearly all uses of DDT have been cancelled.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of DDT = U061.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Action levels for DDT in various food items and in processed animal feed range from 0.05 to 5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 mg/m^3.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 mg/m^3.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 500 mg/m^3.

Recommended exposure limit (time-weighted-average workday) = 0.5 mg/m^3.

Listed as a potential occupational carcinogen.

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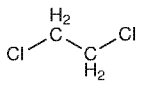
1,2-Dichloroethane

CAS No. 107-06-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as ethylene dichloride



Carcinogenicity

1,2-Dichloroethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,2-dichloroethane caused tumors in mice and rats at several different tissue sites. Administration of 1,2-dichloroethane by stomach tube caused malignant lymphoma and benign lung tumors (alveolar/bronchiolar adenoma) in mice of both sexes, blood-vessel cancer (hemangiosarcoma) in rats of both sexes, mammary-gland cancer (adenocarcinoma) in female mice and rats, uterine cancer (endometrial stromal tumors) in female mice, forestomach cancer (squamous-cell carcinoma) in male rats, and liver cancer (hepatocellular carcinoma) in male mice (NCI 1978).

Since 1,2-dichloroethane was listed in the *Second Annual Report on Carcinogens,* an additional study in rodents has been identified. In mice and rats, inhalation exposure to 1,2-dichloroethane caused mammary-gland tumors in both species and liver and lung tumors in mice (IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,2-dichloroethane. Since 1,2-dichloroethane was listed in the *Second Annual Report on Carcinogens,* additional epidemiological studies have been identified. The International Agency for Research on Cancer reviewed five cohort mortality studies and one nested case-control study of chemical workers with exposure to 1,2-dichloroethane and other chemicals (such as ethylene oxide or chlorohydrin) (IARC 1999). Excesses of lymphatic and hematopoietic cancer were observed in three cohort studies (Hogstedt *et al.* 1979, Benson and Teta 1993, Olsen *et al.* 1997), pancreatic cancer in one study (Benson and Teta 1993), and stomach cancer in one study (Hogstedt *et al.* 1979). No excesses of cancer were found in a fourth cohort study (Sweeney *et al.* 1986) or in a cohort study of brain cancer with a nested case-control study (Austin and Schnatter 1983a,b). Because all of the workers in these studies potentially were coexposed to numerous agents, it is not possible to evaluate excess risks associated specifically with exposure to 1,2-dichloroethane.

Properties

1,2-Dichloroethane is a chlorinated aliphatic hydrocarbon that exists at room temperature as a colorless oily liquid with a sweet, pleasant odor similar to that of chloroform (HSDB 2009). It is slightly soluble in water, soluble in acetone, benzene, and carbon tetrachloride, and miscible with alcohol, chloroform, and ether. 1,2-Dichloroethane is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 1,2-dichloroethane are listed in the following table.

Property	Information
Molecular weight	99.0[a]
Specific gravity	1.2351 at 20°C[a]
Melting point	–35.3°C[a]
Boiling point	83.5°C[a]
Log K_{ow}	1.48[a]
Water solubility	8.6 g/L at 25°C[a]
Vapor pressure	78.9 mm Hg at 25°C[a]
Vapor density relative to air	3.42[b]

Sources: [a]HSDB 2009, [b]Akron 2009.

Use

1,2-Dichloroethane is currently used primarily to produce vinyl chloride (IPCS 1995, IARC 1999). It was formerly used as a solvent for processing pharmaceutical products; as a solvent for fats, oils, waxes, gums, resins, and particularly for rubber; and in paint, varnish, and finish removers (HSDB 2009). It was also used as an insect fumigant for stored grains and in mushroom houses, a soil fumigant in peach and apple orchards, a cleaner for upholstery and carpets, a solvent in textile cleaning and metal degreasing, a lead scavenger in antiknock gasoline, a starting material for chlorinated solvents such as vinylidene chloride, a dispersant for plastics and elastomers such as synthetic rubber, an ore flotation compound, and an extractant in certain food processes (NIOSH 1978, IARC 1979, HSDB 2009). It has been replaced as a solvent and degreaser by less toxic compounds and is no longer registered for use as an insect fumigant in the United States (IARC 1999). Therapeutically, 1,2-dichloroethane formerly was used as a general anesthetic instead of chloroform, especially in ophthalmic surgery (HSDB 2009).

Production

U.S. commercial production of 1,2-dichloroethane was first reported in 1922 (IARC 1979). 1,2-Dichloroethane is a major industrial chemical and ranks among the highest-volume chemicals produced in the United States (EPA 2009a). In 2003, total U.S. annual production capacity for 1,2-dichloroethane was over 35 billion pounds (CMR 2003). In 2009, 1,2-dichloroethane was produced by 95 manufacturers worldwide, including 15 in the United States (SRI 2009), and was available from 67 suppliers, including 35 U.S. suppliers (Chem Sources 2009). U.S. imports of 1,2-dichloroethane peaked at 155 million kilograms (341 million pounds) in 1999, declining to 498,000 kg (1 million pounds) in 2007 and rebounding to 44 million kilograms (96 million pounds) in 2008 (USITC 2009). U.S. exports of 1,2-dichloroethane also peaked in 1999, at 1.2 billion kilograms (2.6 billion pounds), falling to a low of 398 million kilograms (875 million pounds) in 2006. Reports filed every four years under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,2-dichloroethane totaled over a billion pounds from 1986 to 2006 (EPA 2004, 2009b).

Exposure

The routes of potential human exposure to 1,2-dichloroethane are inhalation, ingestion, and dermal contact (IARC 1979). For the general population, the greatest source of exposure is inhalation of contaminated ambient or indoor air, with a minor contribution from ingestion of contaminated drinking water. Releases to the environment may result from the manufacture, use, storage, distribution, and disposal of 1,2-dichloroethane (ATSDR 2001). 1,2-Dichloroethane is also an anaerobic biodegradation product of tetrachloroethane. According to EPA's Toxics Release Inventory, environmental releases of 1,2-dichloroethane peaked in 1990, at 6,525,967 lb, over 5.6 million pounds (85%) of which was released to air. In 2007, 56 facilities released a total of 450,400 lb of 1,2-dichloroethane, of which 334,000 lb (74%) was released to air, 96,568 lb (21%) to land, 17,000 lb (4%) to on-site and off-site underground injection wells, and 2,310 lb (0.5%) to water (TRI 2009). 1,2-Dichloroethane was identified in at least 570 of the 1,585 hazardous-waste sites proposed for inclusion on EPA's National Priorities List; however, the number of sites evaluated for 1,2-dichloroethane was not reported (ATSDR 2001).

1,2-Dichloroethane has been detected in ambient air (urban and rural) and indoor air of residences near hazardous-waste disposal sites and in surface water, groundwater, and drinking water (ATSDR 2001). In the 1980s, mean concentrations of 1,2-dichloroethane in U.S. am-

bient air ranged from 0.33 to 6.05 μg/m^3 (IPCS 1998). EPA reported that 1,2-dichloroethane was present in 53 of 204 surface-water samples taken near heavily industrialized areas across the United States (IARC 1979). Drinking-water samples from a number of urban and rural locations in the United States have been reported to be contaminated with 1,2-dichloroethane. Concentrations in sources of drinking-water supplies were reported to range from trace amounts to 4.8 μg/L in surface water and from trace amounts to 400 μg/L in groundwater. Ingestion of 1,2-dichloroethane in contaminated drinking water is expected to be an important source of exposure for 4% to 5% of the U.S. population. 1,2-Dichloroethane has also been detected in food items and in human breath, urine, and milk (ATSDR 2001).

Occupational exposure to 1,2-dichloroethane now occurs chiefly among workers involved in the production of vinyl chloride (IPCS 1998). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 83,246 workers in 1,526 plants, including 33,361 women, potentially were exposed to 1,2-dichloroethane (NIOSH 1990). The largest numbers of exposed workers were employed in the Chemical and Allied Products, Apparel and Other Textile Products, Business Services, and Petroleum and Coal Products industries as machine operators, assemblers, production inspectors, checkers, and examiners (ATSDR 2001).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,2-dichloroethane on ships and barges.

Department of Transportation (DOT)

1,2-Dichloroethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of 1,2-dichloroethane is subject to certain provisions for the control of volatile organic compound emissions.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Designated a hazardous substance.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.38 μg/L; based on fish or shellfish consumption only = 37 μg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxic characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,2-dichloroethane = U077, F024, F025, K018, K019, K020, K029, K030, K096.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 ppm.
Ethylene dichloride in spice oleoresins when present as a residue from the extraction of spice is allowed in concentrations not to exceed 30 ppm.
Ethylene dichloride residues shall not exceed 150 ppm when used in the production of modified hop extract used in beer.
Ethylene dichloride residues shall not exceed 250 ppm when used as a solvent in the production of the food additive whole fish protein concentrate.
Polyethylenimine polymer may be used as a fixing material in the immobilization of glucoamylase enzyme for use in the manufacture of beer, with residual 1,2-dichloroethane levels not to exceed 1 ppm.
The maximum quantity of ethylene dichloride permitted to remain in or on the extracted by-products in the manufacture of animal feeds is 300 parts per million.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Acceptable peak exposure = 200 ppm (maximum duration = 5 min in any 3 h).
Ceiling concentration = 100 ppm.
Permissible exposure limit (PEL) = 50 ppm.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 ppm.
Recommended exposure limit (time-weighted-average workday) = 1 ppm (4 mg/m^3).
Short-term exposure limit (STEL) = 2 ppm (8 mg/m^3).
Listed as a potential occupational carcinogen.

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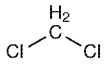
Dichloromethane

CAS No. 75-09-2

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as methylene chloride



Carcinogenicity

Dichloromethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to dichloromethane by inhalation caused tumors in two rodent species and at several different tissue sites. In mice of both sexes, it caused tumors of the lung (alveolar/bronchiolar tumors) and liver (hepatocellular tumors), and in rats of both sexes, it caused benign mammary-gland tumors (fibroadenoma) (NTP 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dichloromethane (IARC 1982). In 1999, the International Agency for Research on Cancer reviewed additional epidemiological studies published after dichloromethane had been listed in the *Fifth Annual Report on Carcinogens,* including seven cohort studies (six of which were small) and three case-control studies (of brain cancer, breast cancer, and rectal plus lung cancer). Although cancer risk was increased for some tissue sites, including the pancreas in two cohort studies, the breast in one case-control and one cohort study, and the liver, prostate, rectum, and brain in one study each, IARC concluded that the evidence for carcinogenicity was too inconsistent to support a causal interpretation (IARC 1987, 1999). Studies published since the IARC review include updates of previous studies (Hearne and Pifer 1999, Dumas *et al.* 2000, Radican *et al.* 2008) and new case-control studies of brain cancer (Cocco *et al.* 1999), lymphoma (Seidler *et al.* 2007), and renal-cell cancer (Dosemeci *et al.* 1999). As was found in the 1999 IARC review, excesses of cancer at specific tissue sites, including the pancreas, lymphohematopoietic system, brain and central nervous system, and breast, were reported in some but not all studies.

Properties

Dichloromethane is a chlorinated hydrocarbon that exists at room temperature as a colorless liquid with a sweet, pleasant odor similar to that of chloroform (NTP 1986). It is miscible with alcohol, ether, dimethyl formamide, and carbon tetrachloride. Dichloromethane is stable at normal temperatures and pressures, but it may form explosive compounds when in a high-oxygen environment (Akron 2009). Physical and chemical properties of dichloromethane are listed in the following table.

Property	Information
Molecular weight	84.9
Specific gravity	1.3255 20°C/4°C
Melting point	–95°C
Boiling point	39.75°C at 760 mm Hg
Log K_{ow}	1.25
Water solubility	13.0 g/L at 25°C
Vapor pressure	435 mm Hg at 25°C
Vapor density relative to air	2.93

Source: HSDB 2009.

Use

Dichloromethane is used as a solvent in paint strippers and removers (30%), in adhesives (20%), as a propellant in aerosols (10%), as a solvent in the manufacture of pharmaceuticals and drugs (10%), in chemical processing (10%), as a metal cleaning and finishing solvent (10%), and in urethane foam blowing (5%) (Holbrook 2003). Other uses make up the remaining 5%. Dichloromethane has also been used as a solvent in the production of triacetate fibers, in film processing, and as an extraction solvent for spice oleoresins, hops, and caffeine in coffee (NTP 1986). However, due to health concerns, dichloromethane's use as an extraction solvent in food products and coffee has declined greatly over the years (ATSDR 2000). It is also used as a low-pressure refrigerant, for air-conditioning installations, and as a low-temperature heat-transfer medium (Holbrook 2003). Current household products that may contain dichloromethane include lubricants, valve cleaners, and degreasers for automobiles, adhesive and varnish removers, paint strippers, and one household herbicide (HPD 2009). Dichloromethane is present in these products at percentages ranging from 1% to 90%. Dichloromethane was once registered for use in the United States as an insecticide for commodity fumigation of strawberries, citrus fruits, and a variety of grains (ATSDR 2000). It is no longer an active ingredient in any registered pesticide product in the United States (HSDB 2009).

Production

In 2009, dichloromethane was produced by 26 manufacturers worldwide, including 4 in the United States (SRI 2009), and was available from 133 suppliers, including 58 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of dichloromethane totaled 500 million to 1 billion pounds in 1986 and 1990 and 100 million to 500 million pounds between 1996 and 2006 (EPA 2004, 2009). From 1989 to 2008, U.S. exports of dichloromethane exceeded imports; in 2008, imports were over 19.8 million pounds, and exports were 136.9 million pounds (USITC 2009).

Exposure

The routes of potential human exposure to dichloromethane are inhalation, ingestion, and dermal contact (NTP 1986). However, absorption is slower after dermal contact than after ingestion or inhalation. The general population is exposed mainly through inhalation of ambient air. Inhalation exposure might also occur through the use of consumer products containing dichloromethane, such as paint removers, which results in relatively high concentrations in indoor air (IPCS 1996, ATSDR 2000). Dichloromethane was found in 43.7% of 1,159 consumer household products tested and in 74.3% of paint-related products, at an average concentration of 33.5% (Sack *et al.* 1992). According to EPA's Toxics Release Inventory, environmental releases of dichloromethane totaled nearly 139 million pounds in 1988. In 2007, over 5.9 million pounds was released by 297 facilities, including over 5 million pounds to air, for a decrease of over 95% since 1988 (TRI

2009). In rural and remote areas, dichloromethane was measured in ambient air at concentrations of 0.07 to 0.29 μg/m^3; in suburban areas, the average concentration was less than 2 μg/m^3, while in urban areas it was no more than 15 μg/m^3. Near hazardous-waste sites, concentrations of up to 43 μg/m^3 were recorded (IPCS 1996).

Dichloromethane occurs in groundwater, finished drinking water, commercially bottled artesian-well water, and surface water in heavily industrialized river basins. Higher levels of dichloromethane typically are found in groundwater than surface water. Dichloromethane was the sixth most frequently detected organic contaminant in groundwater from hazardous-waste sites in 1987, occurring at 19% of the sites (ATSDR 2000). In a study published in 2007, dichloromethane was detected in 3% of over 5,000 groundwater samples taken in the United States between 1985 and 2002. The concentrations ranged from 0.02 to 100 μg/L, with a median well below the Safe Drinking Water Act maximum contaminant level of 5 μg/L (Moran *et al.* 2007).

Occupational exposure to dichloromethane occurs during its production and shipping, primarily during filling and packaging. Because of its use in paint strippers, exposure also occurs during formulation of paint removers, original equipment manufacture, and commercial furniture refinishing (IPCS 1996). In the 1980s, dichloromethane was found in the air at an Israeli workplace at a concentration of 5.22 ppm and in urine samples from seven workers at a maximum concentration of 0.06 mg/L (Hoffer *et al.* 2005). In the 1990s, health-hazard investigations by the National Institute for Occupational Safety and Health found workplace air concentrations of 0.17 ppm to 525 ppm, with a median of 5 ppm (Armstrong and Green 2004). In field monitoring of workers in a waste-repackaging facility, dichloromethane was detected in 7 of 16 samples of exhaled breath at concentrations of up to 573 ppm (Thrall *et al.* 2001). In 2003, the American Conference of Governmental Industrial Hygienists recommended that a urinary concentration of 200 μg/L at the end of a shift be used to monitor the threshold limit value of 50 ppm in workplace air (Imbriani and Ghittori 2005). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,438,196 workers, including 352,536 women, potentially were exposed to dichloromethane (NIOSH 1990). No more recent large occupational exposure surveys were identified.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of dichloromethane on ships and barges.

Consumer Product Safety Commission (CPSC)

Products containing dichloromethane must be labeled to indicate that inhalation of vapor has produced cancer in laboratory animals and must also specify precautions.

Department of Transportation (DOT)

Dichloromethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 4.6 μg/L; based on fish or shellfish consumption only = 590 μg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of dichloromethane = U080, F001, F002, F024, F025, K009, K010, K156, K157, K158.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.
Dichloromethane may be used as an extraction solvent to prepare modified hop extract, spice oleoresins, and coffee, with limitations prescribed in 21 CFR 172 and 173.
Dichloromethane is banned from use in cosmetic products.
Polyestercarbonate resins may be safely used in articles intended for use in producing, packaging, or holding foods with residual methylene chloride levels not to exceed 5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 25 ppm.
Short-term exposure limit (STEL) = 125 ppm.
Comprehensive standards for occupational exposure to this substance have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 50 ppm.

Consumer Products Safety Commission (CPSC)

Requests that manufacturers eliminate the use of hazardous chemicals, including dichloromethane, in children's products.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,300 ppm.
Listed as a potential occupational carcinogen.

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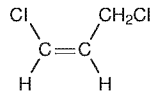
1,3-Dichloropropene (Technical Grade)

CAS No. 542-75-6

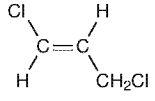
Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as Telone II soil fumigant, a registered trademark of Dow Agrosciences



cis-1,3-dichloropropene
(*Z*)-1,3-dichloropropene



trans-1,3-dichloropropene
(*E*)-1,3-dichloropropene

Carcinogenicity

Technical-grade 1,3-dichloropropene (containing 1.0% epichlorohydrin as a stabilizer) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. The technical-grade 1,3-dichloropropene used in the cancer studies in experimental animals was a mixture of *cis*- and *trans*-isomers and varied in purity and the stabilizer used (see Properties).

Cancer Studies in Experimental Animals

Oral exposure to technical-grade 1,3-dichloropropene (Telone II, approximately 89% pure, containing 1.0% epichlorohydrin as a stabilizer) caused tumors at several different tissue sites in rats and mice. Administered by stomach tube, technical-grade 1,3-dichloropropene caused benign and/or malignant tumors of the forestomach (squamous-cell papilloma or carcinoma) in rats of both sexes and in female mice. It also caused urinary-bladder cancer (transitional-cell carcinoma) and benign lung tumors (alveolar/bronchiolar adenoma) in female mice and benign liver tumors (adenoma) in male mice. The same types of tumors observed in female mice (forestomach, urinary-bladder, and lung tumors) also were observed in male mice; however, the evidence for carcinogenicity in males was considered to be inadequate because of low survival in the vehicle-control group (NTP 1985). *cis*-1,3-Dichloropropene administered by subcutaneous injection caused tumors at the injection-site (fibrosarcoma) in female mice (Van Duuren *et al.* 1979).

Since technical-grade 1,3-dichloropropene was listed in the *Fifth Annual Report on Carcinogens,* studies in rodents have been identified that evaluated the carcinogenicity of technical-grade 1,3-dichloropropene without the stabilizer epichlorohydrin. Inhalation exposure to technical-grade 1,3-dichloropropene (92.1% pure, stabilized with 2% epoxidized soybean oil) caused benign lung tumors (alveolar/bronchiolar adenoma) in male mice (Lomax *et al.* 1989, IARC 1999). Dietary exposure to 1,3-dichloropropene (Telone II, 96% pure, stabilized with 2% epoxidized soybean oil) microencapsulated in a starch-sucrose matrix caused benign liver tumors (hepatocellular adenoma) in rats of both sexes (Stebbins *et al.* 2000).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,3-dichloropropene. Two cases of malignant histiocytic lymphoma were reported among nine firemen accidentally exposed to 1,3-dichloropropene six years before diagnosis, and one case of leukemia was reported in a farmer exposed to 1,3-dichloropropene (IARC 1986, 1987). Since technical grade 1,3-dichloropropene was listed in the *Fifth Annual Report on Carcinogens,* an ecological case-control study of pancreatic cancer mortality (from 1989 to 1996) and exposure to organochlorine pesticides was reported. The authors reported an increase in pancreatic cancer mortality among long-term residents in areas with high application rates of 1,3-dichloropropene after adjustment for the use of other pesticides (Clary and Ritz 2003).

Properties

1,3-Dichloropropene, a chlorinated alkene, exists at room temperature as a clear colorless to straw-colored liquid with a chloroform-like odor (NTP 1985, IARC 1986). It is slightly soluble in water and soluble in methanol, chloroform, acetone, diethyl ether, toluene, benzene, *n*-heptane, and octane. It is stable at normal temperatures in closed containers, but is considered highly flammable (Akron 2009). Technical-grade formulations of 1,3-dichloropropene contain mixtures of cis (Z) and trans (E) isomers (EPA 2000). Physical and chemical properties of 1,3-dichloropropene are listed in the following table.

Property	Technical	Cis	Trans
Molecular weight	111.0	111.0	111.0
Specific gravity	1.220 at 25°C	1.224 at 20°C	1.224 at 20°C
Melting point	< –50°C	NR	NR
Boiling point	108°C	104°C	112°C
Log K_{ow}	1.82	2.06	2.03
Water solubility	2.8 g/L at 20°C	2.7 g/L at 25°C	2.8 g/L at 25°C
Vapor pressure	34 mmHg at 25°C	26 mmHg at 20°C	34 mmHg at 25°C
Vapor density relative to air	3.8	1.4	1.4

Source: HSDB 2009. NR = not reported.

The technical-grade formulation of 1,3-dichloropropene (Telone II) used in the National Toxicology Program cancer studies in rodents contained 88% to 90% 1,3-dichloropropene (41.6% cis, 45.9% trans), 2.5% 1,2-dichloropropene, 1.5% of a trichloropropene isomer, other impurities, and 1% epichlorohydrin as stabilizer (NTP 1985). The inhalation-exposure study (Lomax *et al.* 1989) used a formulation

containing 92.1% 1,3-dichloropropene (49.5% cis, 42.6% trans), 0.7% 1,2-dichloropropane, and mixtures of hexanes and hexadienes, stabilized with 2% epoxidized soybean oil. The formulation used in the dietary-exposure study (Stebbins *et al.* 2000) contained 96% 1,3-dichloropropene (50.7% cis, 45.1% trans), stabilized with 2% epoxidized soybean oil; no information on impurities was reported. Other formulations of pesticides based on 1,3-dichloropropene may also contain 1,2-dichloropropane, trichloronitromethane, 1,2-dibromoethane, or methyl isothiocyanate (IARC 1986, HSDB 2009).

Use

1,3-Dichloropropene (a technical-grade mixture of the *cis*- and *trans*-isomers) is used as a preplanting fumigant, mainly for the control of nematodes affecting the roots of plants, selected plant diseases, garden centipedes, wireworms, and weeds; as a solvent; and as an intermediate in the manufacture of 3,3-dichloro-1-propene and other pesticides. It is registered for use on all vegetable, fruit, and nut crops, all forage crops, tobacco, all fiber crops, and all nursery crops (EPA 1998). In Hawaii, 1,3-dichloropropene is used to control nematodes on pineapples at planting (Albrecht 1987). In 2009, three products containing 1,3-dichloropropene as an active ingredient were registered for restricted, non-residential use in the United States (EPA 2009). No products containing 1,3-dichloropropene are registered for use by homeowners (EPA 1998).

Production

1,3-Dichloropropene was first synthesized in 1872, and commercial production in the United States started in 1955 (NTP 1985, IARC 1986). Before 1978, annual U.S. production was 25 million kilograms (55 million pounds) (NTP 1985). In 2009, 1,3-dichloropropene was produced by one manufacturer each in the United States and East Asia and two manufacturers in Europe (SRI 2009) and was available from 21 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,3-dichloropropene or Telone II were found. Reports filed from 1986 to 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,3-dichloropropene totaled 1 million to 10 million pounds (EPA 2004).

Exposure

The primary routes of potential human exposure to 1,3-dichloropropene are inhalation, dermal contact, and ingestion (NTP 1985, ATSDR 1992, EPA 1998). In 1978, 1 million kilograms (2.2 million pounds) of pesticide containing 1,3-dichloropropene was reportedly used in California (ATSDR 1992). In Hawaii, estimated usage on pineapple fields based on the usual application rate for Telone II was nearly 0.9 million kilograms (2 million pounds) in 1985 (Albrecht 1987). Although the data are incomplete, it has been estimated that from 1987 to 1995, over 23 million pounds of 1,3-dichloropropene was applied as a soil fumigant nationwide (EPA 1998). 1,3-Dichloropropene has not been detected in food crops grown in treated soils.

EPA's Toxics Release Inventory reported environmental releases of almost 55,000 lb of 1,3-dichloropropene in 1988. Releases have steadily declined since then; in 2009, 16 industrial facilities released 5,695 lb. Most releases have been to air (TRI 2009). 1,3-Dichloropropene can also be formed from chlorination of organic material during water treatment. In air, 1,3-dichloropropene is degraded by photochemically produced hydroxyl radicals, with a half-life of 7 hours for the *trans*-isomer and 12 hours for the *cis*-isomer. It is also degraded by reaction with ozone, with a half-life of 12 to 52 days. Volatilization of 1,3-dichloropropene from a model river was estimated to occur with a half-life of 4 hours (HSDB 2009). In field studies, 25% of 1,3-dichloropropene volatilized within two weeks after soil injection (EPA 1998). The 1,3-dichloropropene remaining in moist soils may hydrolyze at rates depending on temperature; the reported half-life was 13.5 days at 20°C, 2 days at 29°C, and 100 days at 2°C. Absorption by soil and sediment is expected to be low, based on physical and chemical properties and laboratory data. Monitoring data show that 1,3-dichloropropene is highly mobile in soils (ATSDR 1992, EPA 1998, HSDB 2009). Biodegradation by Pseudomonas spp. is expected to occur in soil, with a half-life of 1 to 3 days (NTP 1985). Hydrolysis and biodegradation products are mostly 3-chloroallyl alcohol and, to a lesser extent, 3-chloroacrylic acid (NTP 1985, ATSDR 1992, EPA 1998). The potential for 1,3-dichloropropene or its degradation products to bioaccumulate in terrestrial or aquatic organisms is low, based on physical and chemical properties. This is consistent with the finding that only 1% of radiolabeled 1,3-dichloropropene administered orally remained in rats after 4 days (NTP 1985, HSDB 2009).

1,3-Dichloropropene was measured in ambient air at distances of 0 to 800 m from treated fields at mean seven-day air concentrations ranging from 11 to 181 μg/m^3 (EPA 1998). In another study, the median air concentration of *cis*-1,3-dichloropropene was 23.9 ppb by volume in 148 urban air samples collected from representative locations (ATSDR 1992). During field application of the nematocide in the Netherlands, 8-hour time-weighted-average concentrations were up to 1,120 μg/m^3 for the *cis*-isomer and 910 μg/m^3 for the *trans*-isomer (van Welie *et al.* 1991). 1,3-Dichloropropene was measured in a drinking-water aquifer at average concentrations of up to 357 ppb (micrograms per liter) and in surface water at up to 1.8 ppb (EPA 1998). It was detected at very low levels (up to 18 μg/L) in groundwater contaminated by leachates from municipal landfills and was identified at 107 hazardous-waste sites on EPA's National Priorities List (ATSDR 1992). Samples of rainwater were reported to contain up to 12 ng/L of 1,3-dichloropropene (10 ng/L of the *cis*-isomer and 2 ng/L of the *trans*-isomer). In one study, water entering a treatment facility did not contain detectable levels of 1,3-dichloropropene, but after chlorination, 1,3-dichloropropene was found in the resulting liquid sludge at a concentration of 10 ppb (HSDB 2009).

Workers may be exposed to 1,3-dichloropropene during its manufacture or during formulation or application of the pesticide products. Measured exposure of agricultural workers was highest during loading (mean concentration = 10,833 μg/m^3) and lower during application (mean concentration = 1,359 μg/m^3) (EPA 1998). Dermal exposure has been shown to occur even with the use of most types of protective gloves (Zainal and Que Hee 2005). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,162 workers, including 33 women, potentially were exposed to 1,3-dichloropropene in the Chemical, Petroleum, and Coal Products industries (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for the safe transport of 1,3-dichloropropene on ships and barges.

Department of Transportation (DOT)

Dichloropropenes are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.
Effluent Guidelines: Listed as a toxic pollutant.